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Electrochemical Use of Chiral Non-Racemic Diselenides

Matthew Cox

A Thesis Submitted for the Degree of Doctor of Philosophy at Cardiff University

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Acknowledgments

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I would also like to thank my family and friends for their patience and encouragement throughout my studies.

The biggest thanks of all to Alison.

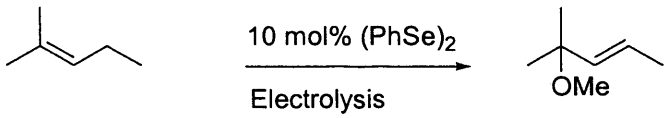
List of Abbreviations

$[\alpha]_D$	specific optical rotation
Ar	aromatic substituent
t-Bu	tertiary butyl
n-Bu	butyl
de	diastereomeric excess
c	concentration
calcd.	calculated
CV	cyclic voltammetry
DEPT	distortionless enhancement by polarisation transfer
DCM	dichloromethane
DIP-Cl	Chlorodiisopinocampheylborane
e^-	an electron
ee	enantiomeric excess
EI	electronic ionisation
eq.	equivalents
Et	ethyl
GP	general procedure
GC	gas chromatography
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
hr	1 hour
IR	infrared spectra
J	NMR coupling constant
mbar	millibar
Me	methyl
min	minute
MPLC	medium pressure liquid chromatography
MOM	methoxymethyl
m/z	mass to charge ratio
MS	mass spectrometry
NMR	nuclear magnetic resonance

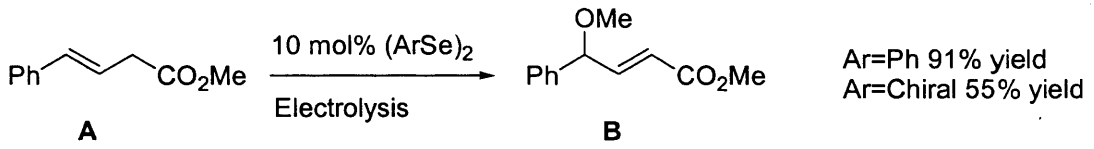
ox	oxidised
Ph	phenyl
psi	pounds per square inch
red	reduced
R*f*	retention factor
rt	room temperature
TEAB	tetraethylammonium bromide
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
Ts/tosyl	*para*-toluenesulphonyl
v/v	volume by volume

Summary

An electrochemical approach has previously been described for the selenenylation-deselenenylation of alkenes using diphenyl diselenide. The use of electrochemistry enabled diphenyl diselenide to be used in catalytic amounts to convert alkenes into allylic ethers.



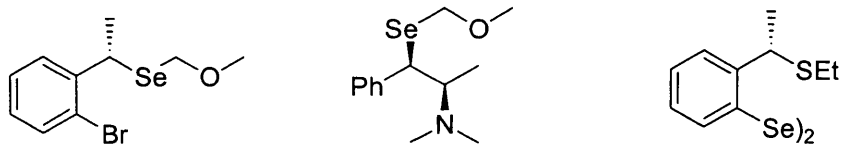
The electrochemical use of diselenides bearing a chiral side chain has now been investigated. The initial investigations involved the use of diphenyl diselenide, in conditions which varied considerably from those described previously in the literature. By using just 10 mol% diphenyl diselenide, the conversion of alkene **A** into allylic ether **B** was achieved in 91% yield.



A **B**

Having established viable conditions using diphenyl diselenide, a range of chiral non-racemic diselenides was now used for the same conversion. Mixed results were obtained, with yields of **B** ranging from 19% to 55% and selectivities ranging from 0% to 69% *ee*. The reaction of several chiral diselenides was investigated in depth and a likely mechanism for the addition elimination sequence proposed.

The investigation was widened to include more alkenes and different reaction conditions, though no alkenes proved as ideal a substrate as **A**. In an attempt to improve the efficiency of these electrochemical reactions, the synthesis of novel diselenides incorporating new design principles was undertaken, resulting in the synthesis of diselenide **C** which provided the highest selectivity in the electrochemical reaction.



C

Contents

Chapter 1

Introduction

1.1 Organic Electrochemistry

Despite the thousands of organic electrochemical processes that have been discovered since Kolbe first published the electrochemical oxidation of a carboxylic acid to a dimeric alkane and CO_2 in 1849, organic electrochemistry has remained a relatively overlooked technique in organic synthesis.[1,2] It does, however, enable many organic transformations to take place under considerably milder conditions than their non-electrochemical approaches, hence the ongoing interest in developing this area.

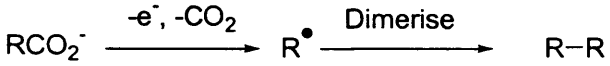


Figure 1-1 The Kolbe reaction[3]

There are a number of important industrial electroorganic processes covering a range of electrochemical reactions. The best known of these processes is the electrohydrodimerisation of acrylonitrile to adipodinitrile, known as the "Monsanto" process.[4] Global production capacity by this technique is several hundred thousand tons per annum, this process representing the biggest success story of organic electrochemistry to date.[5]

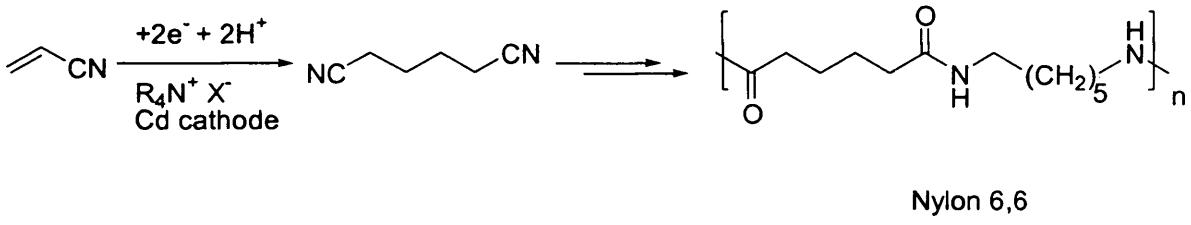


Figure 1-2 The Monsanto process for the electrohydrodimerisation of acrylonitrile

Adipodinitrile is a key intermediate in the synthesis of nylon 6,6 for which it is reduced to hexamethylenediamine before reaction with adipoyl chloride. Other compounds synthesised industrially include Fenoprofen (an analgesic)[6], dihydrophthalic acid (an

intermediate for gasoline additives and plasticizers)[7], a range of aromatic aldehydes (by anodic methoxylation of substituted toluenes)[8] and Acetoin (by anodic methoxylation of cyclohexanone) (Figure 1-3).[9] Industrial electrochemical processes require such specialised knowledge and expertise that they are generally restricted to specialist companies or larger companies with a strong tradition of electrochemistry.

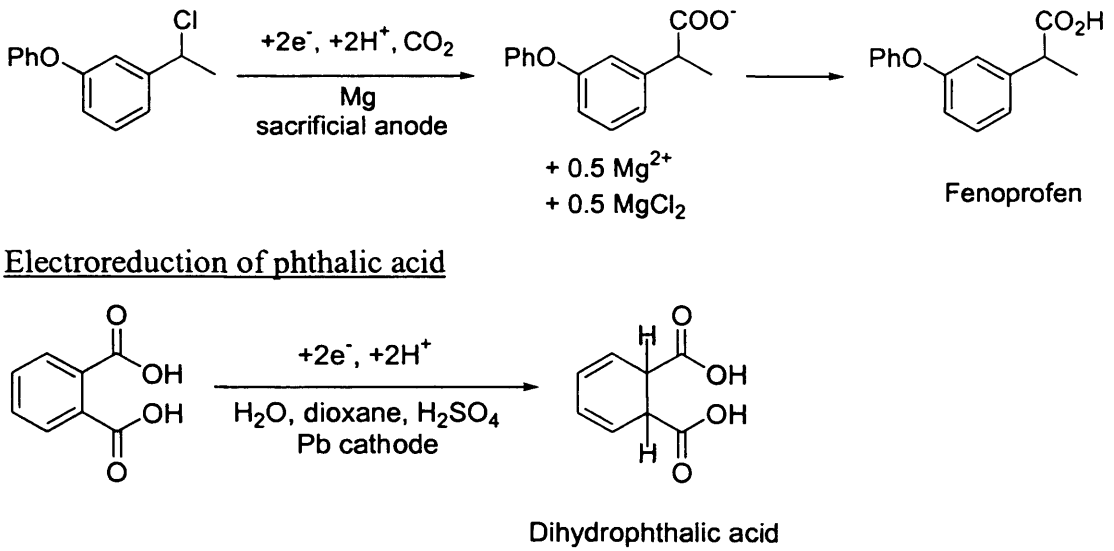


Figure 1-3 Industrial electrochemical processes

On the laboratory scale, electrochemistry can be used to probe mechanistic aspects of organic reactions associated with electron transfer at an electrode, yielding valuable information about reaction pathways and kinetics.[10] A unique feature of these methods

is the use of the electrode both as a means of initiating a reaction and as the means of monitoring the reaction.

Although organic electrochemistry has developed rapidly since the 1960s, its stereochemical aspects have advanced very slowly. Reasons for this include the complex manner of stereo control in general and of the unique heterogeneous interface between an electrode and the solution.[11] As methods for analysing mixtures of isomers have become more available the stereochemical aspect of electrochemistry is receiving more and more attention. The extremely strong electric field (around 10^8 Vcm^{-1}) present in the innermost layer of the solution that surrounds the electrode is likely to cause a unique variety of polar effects on solvated molecules as well as adsorbed species.[12] The orientation of polar adsorbed species is electrostatically influenced and so the stereochemistry of the reaction may also be influenced. The conformational and configurational stability of the intermediates is a key factor in determining the overall stereochemical outcome of a given reaction and these stabilities will be readily influenced by electrostatic factors. Stereoselective reactions are best optimised by empirical rather than theoretical or mechanistic procedures due to the complexities of stereocontrol in electrochemical reactions.[13]

Aside from the examples of stereochemical induction at the electrode, there are numerous examples where the indirect use of an electrode initiates a stereoselective reaction.[14] Systems of this nature require mediators to carry electrons between the electrodes and the solvated substrates, enabling electron transfer to less electroactive organic derivatives. Popular mediators for this type of reaction include metal cations and halides.

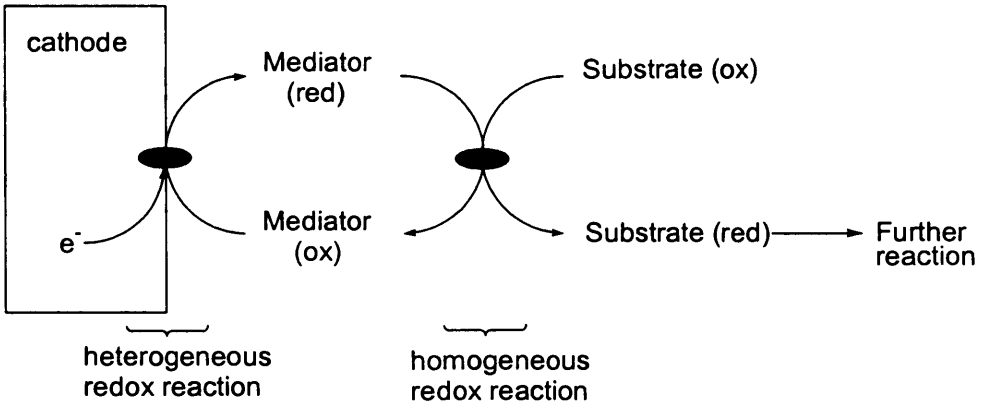


Figure 1-4 The role of an electron mediator

An example of a reaction using a metal cation as an electron mediator is the conversion of aromatic compounds into quinones mediated by ceric ions, in a two-phase oxidative system.[15] The oxidant is regenerated by oxidation at the anode.

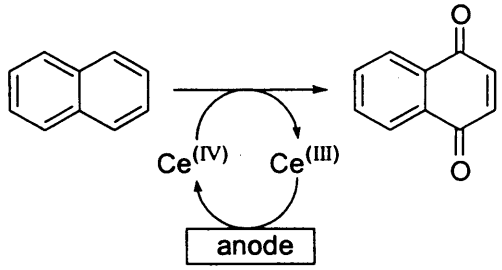


Figure 1-5 Conversion of naphthalene into 1,4-naphthoquinone

A good example of a double-mediator system was published by Torii *et al*, for the asymmetric dihydroxylation of alkenes using the Sharpless ligand.[16] Torii found that iodine could be used as an efficient co-oxidant for osmate recycling, the iodide anion formed being oxidised at the anode back to I_2 and reacted with the next equivalent of osmate. Thus styrene could be oxidised to the diol in 89% yield and 91% *ee*.

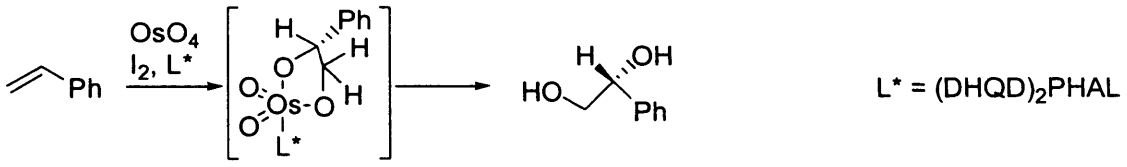


Figure 1-6 Electrochemical use of the Sharpless ligand in the dihydroxylation of styrene[17]

1.2 Selenium in Electrochemistry

Compounds of sulphur, and to a lesser extent selenium, have been studied in some detail and several useful syntheses are described.[18]

The use of selenium in organic electrochemistry can be divided into two distinct groups:

1. Reduction at the cathode to generate compounds of the nature RSe^- or $RSeR^-$.

2. Oxidation at the anode to generate compounds of the nature RSe^+ or $RSeR^+$.

The second group has been the most extensively investigated, research fuelled by the various levels of success attained using the sulphur analogues of organoselenium compounds.[19] An example of the second group is the α-functionalisation of selenides **1** by Fuchigami, following his success in the anodic acetoxylation of sulphides.[20] The paper describes an electrochemical method for the acetoxylation of various selenides possessing an electron withdrawing group.

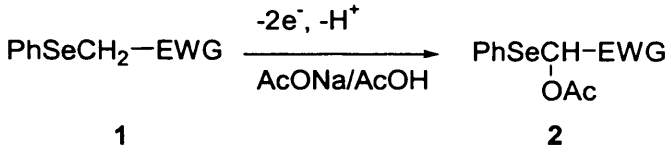


Figure 1-7 Oxidation of selenides to selenoacetals

This acetoxylation reaction is well known with arenes, amines and to a lesser extent sulphides, though only these examples exist for selenides.[21] This route provides a mild route to synthetically useful selenoacetals **2** avoiding complex procedures and special reagents.[22]

It has also been shown that phenylselenenyl carbonyl compounds **3** can be synthesised by the electrochemical oxidation of diphenyl diselenide.[23] Non-electrochemical routes to these products require the use of strong bases and activated selenenylating agents.[24] The electrochemical approach is carried out in neutral conditions where the activated selenenylating agent is generated *in situ* from diphenyl diselenide and a bromide source. The electrochemically-generated bromonium reacts with diphenyl diselenide to form phenylselenenyl bromide. This then attacks the enol form of the carbonyl compound, producing the α-phenylselenenyl carbonyl compound. Compounds of this nature have been used extensively in organic synthesis.[25]

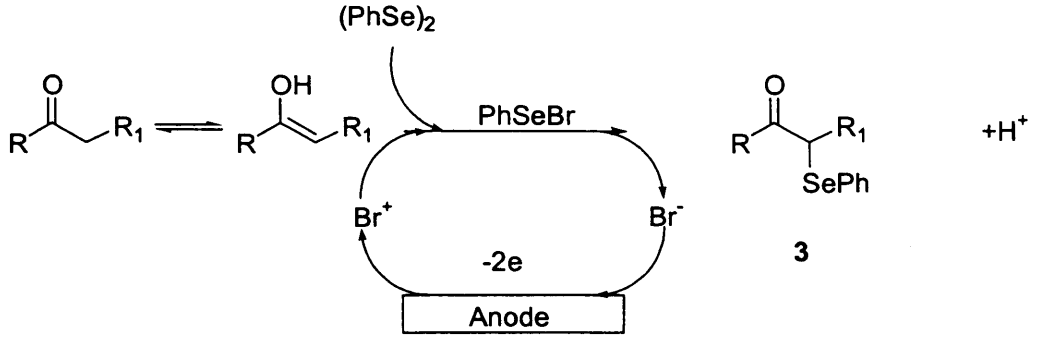


Figure 1-8 Reaction of electrochemically generated phenylselenenyl bromide with enols

Similarly, electrolysis of diphenyl diselenide in the presence of acetonitrile and an alkene was found to give the corresponding acetamidoselenide.[26] This is the first example of the direct addition of selenium and nitrogen to a double bond, a synthesis that has since been achieved using non-electrochemical methods.[27]

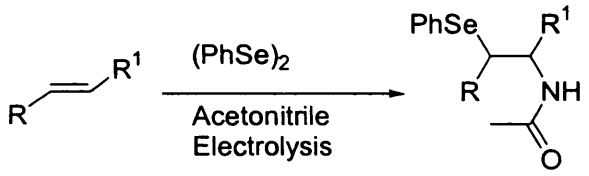


Figure 1-9 Electrochemical synthesis of acetamidoselenides

New conversions were found to be possible using this approach, including the selenohydroxylation of alkynes, unachievable by conventional synthesis.[28] This reaction takes advantage of the precise control offered by electrochemistry to gradually produce phenylselenenic acid, an activated selenenylating agent, avoiding unwanted disproportionation to the unreactive phenylseleninic acid.[29] The enol **4** thus formed spontaneously undergoes elimination of water to give the α-arylseleno-α,β-unsaturated aldehyde **5**.

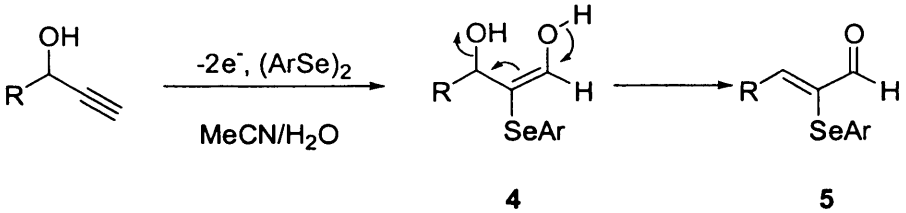


Figure 1-10 Selenohydroxylation of reaction of alkynes

The electrochemical approach also permits the use of higher temperatures where the triple bond is more reactive. At these higher temperatures activated selenenylating agents are generally unstable.

An extension of this methodology to the transformation of arylmethyl ketones into the corresponding α-ketoacetals has had limited success.[30] The low yields (up to 28%) obtained were attributed to practical experimental difficulties including diffusion of reactants through the diaphragm of the divided cell, illustrating some of the hurdles that the synthetic electrochemist must overcome when transferring even a well know reaction from the chemical to the electrochemical approach.

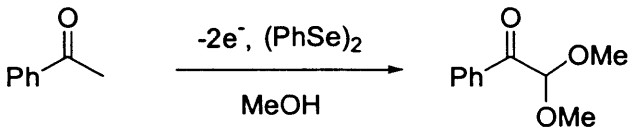


Figure 1-11 Electrochemical transformation of arylmethyl ketones into α-ketoacetals

Another reaction that falls into the second class is exemplified by the electroreductive ring opening of α,β-epoxy carbonyl compounds by diphenyl diselenide.[31] In this example, it is the cathode that is used to generate the reactive species by reducing diphenyl diselenide to phenyl selenolate. The selenolate reacts with an α,β-epoxy carbonyl in the position α to the carbonyl, cleaving the α-carbon oxygen bond. Subsequent nucleophilic attack of a second phenylselenolate on the phenylseleno moiety results in the formation of the hydroxy carbonyl **6** together with diphenyl diselenide.

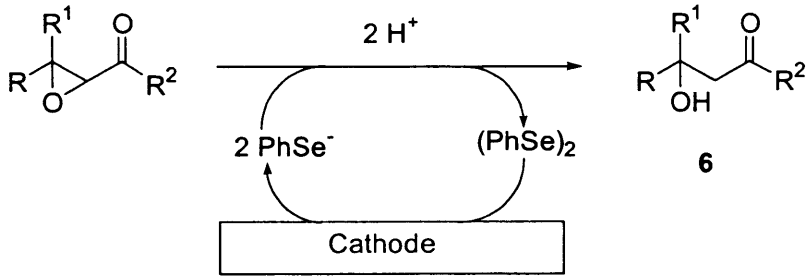


Figure 1-12 Catalytic use of diphenyl diselenide for the electrochemical opening of epoxides

The diphenyl diselenide can therefore be used in catalytic quantities. Yields of up to 85% were obtained using only 2 mol% of diphenyl diselenide. The direct electrochemical reduction of these compounds proceeds considerably less efficiently than the selenium mediated approach.

The most synthetically useful of the electrochemical selenium reactions discovered to date is the electrochemical oxyselenenylation deselenenylation of alkenes by Torii.[32] This method enables the one step transformation of alkenes into allylic ethers and alcohols. This is another example of a reaction involving an electron mediator, in this case bromide, supplied by the use of tetraethylammonium bromide. According to Torii, the bromide is oxidised to bromonium, which reacts with diphenyl diselenide to form the phenylselenenyl bromide, an activated selenenylating agent. Reaction of the phenylselenenyl bromide with an alkene produces the addition product **7**, which is electrochemically oxidised to the corresponding selenoxide. The selenoxide immediately undergoes *syn*-elimination to the allylic ether or alcohol **8**.

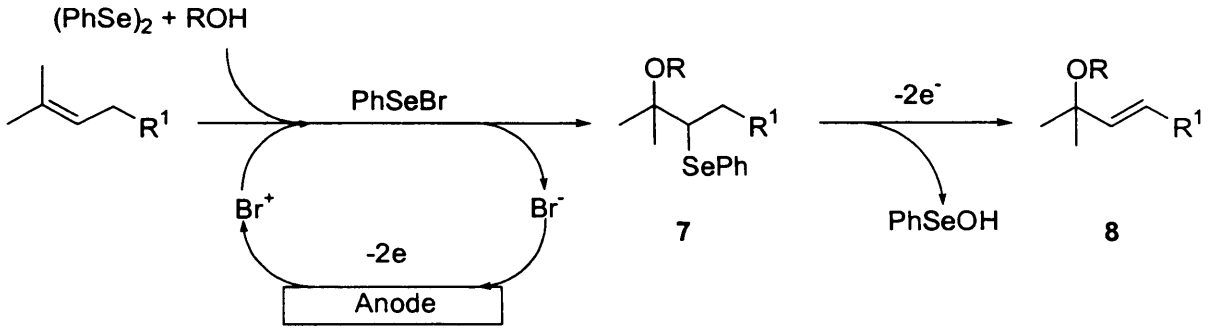
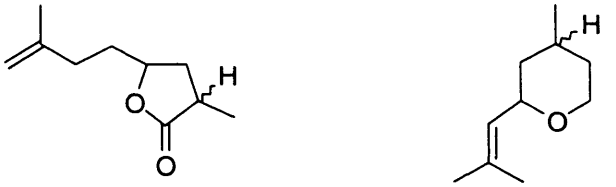


Figure 1-13 Bromide mediated electrochemical oxyselenenylation deselenenylation of alkenes

Using this method, the key steps in the synthesis of the natural products *dl*-marmelolactone **9** and *dl*-rose **10** oxide were achieved in high yields.[22]



9 **10**

Figure 1-14 The natural products synthesised by the electrochemical sequence described

Further studies on electrochemical selenolactonisation reactions of unsaturated acids have also been reported.[33] In this example, a graphite anode and copper cathode were used to synthesise 5-membered and 6-membered lactones in moderate to good yields.

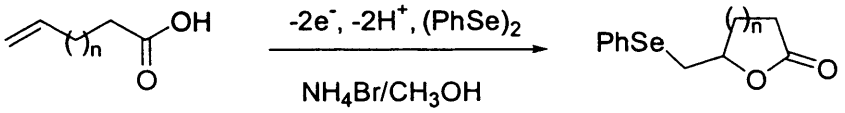


Figure 1-15 Electrochemical selenolactonisation reactions of unsaturated acids

The most significant example of this oxyselenenylation deselenenylation sequence was published by Torii where the electrochemically generated selenium reagent is electrochemically recycled *in situ*.[34]

With careful control of the conditions, disproportionation and overoxidation of the phenylselenenic acid to the inert phenylseleninic acid were avoided, enabling the phenylselenenic acid to react with another equivalent of alkene. Yields of up to 91% were achieved using 10 mol% of diphenyl diselenide.

Given that these electrochemical reactions took place before the advent of the chiral selenium reagent, the possibility for the use of these approaches in asymmetric synthesis have yet to be investigated.

1.3 Selenium Electrophiles

Organoselenium compounds are widely used in organic synthesis as versatile intermediates.[35] Selenium is normally found in the bivalent state in organic compounds

though tetravalent species can be synthesised by the use of strong oxidising agents.[36] By comparison with carbon-sulphur bonds, carbon-selenium bonds are typically weaker. Selenium can be introduced into a molecule as a radical, nucleophile or electrophile using a variety of techniques. Subsequent manipulation of such compounds is often achieved under milder conditions than their sulphur analogues, particularly oxidative elimination of the selenium moiety, a characteristic that dominates the use of selenium in organic chemistry.[37] The selenium moiety can also be eliminated by treatment with a suitable nucleophile or by a radical cleavage reaction.[38] Selenium stabilized carbanions are valuable intermediates in organic synthesis.

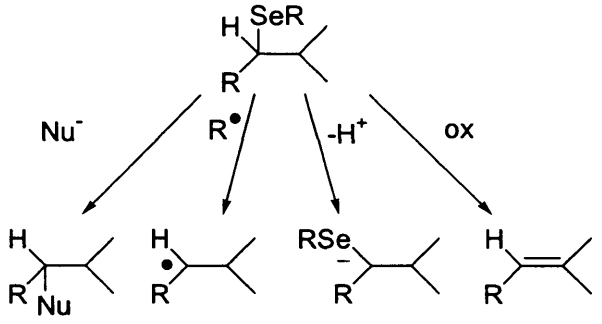


Figure 1-16 Synthetic diversity of organoselenium compounds

Though the use of selenium dioxide as an oxidant was first patented by I.G.Farbenindustrie AG in 1929, it was the discovery of the selenoxide elimination as a mild method for the synthesis of alkenes in 1970 that represents the first milestone in the use of selenium in organic synthesis.[39] This reaction is several orders of magnitude more rapid than the elimination of the corresponding sulphoxides.

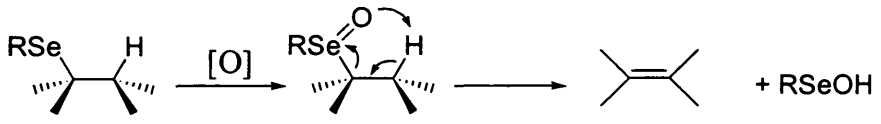


Figure 1-17 The selenoxide elimination as a method for the synthesis of alkenes

The first chiral selenium reagent was synthesised by Tomoda in 1988 based on binaphthyl diselenide **11** (Figure 1-22).[40] Since then a large number of chiral diselenides have been synthesised encompassing an interesting variety of structural

motifs, some more efficient than others.[41] Some of these reagents can be prepared in a few steps from commercially available starting materials, but many require longer synthetic pathways. The most commonly employed electrophilic selenium compounds are the selenenyl halides. Selenenyl halides are prepared from the corresponding diselenides by treatment with bromine or thionyl chloride although some simple selenenyl halides are commercially available. The reactivity of the electrophile can be varied by exchange of the counter-ion, typically by treatment with the appropriate silver salt.[42]

Figure 1-18 Generation of a selenium electrophile from diaryl diselenide

The reaction between an activated selenenylating agent and an alkene results in the highly reactive seleniranium cation. This reaction is analogous to the attack of more familiar electrophiles, such as bromine, iodine, mercury and sulphur electrophiles. The seleniranium cation is attacked by a suitable nucleophile leading exclusively to the *trans* addition product.

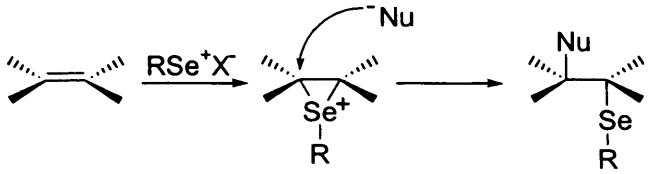


Figure 1-19 Reaction of a selenium electrophile with an alkene

This addition rigidly follows Markownikoff's rule which predicts that the nucleophile will add to the most highly substituted carbon atom. Careful choice of the alkene in this reaction enables the formation of one or two new chiral centres. The use of chiral selenium electrophiles seeks to exploit this by directing the stereochemistry at these positions.

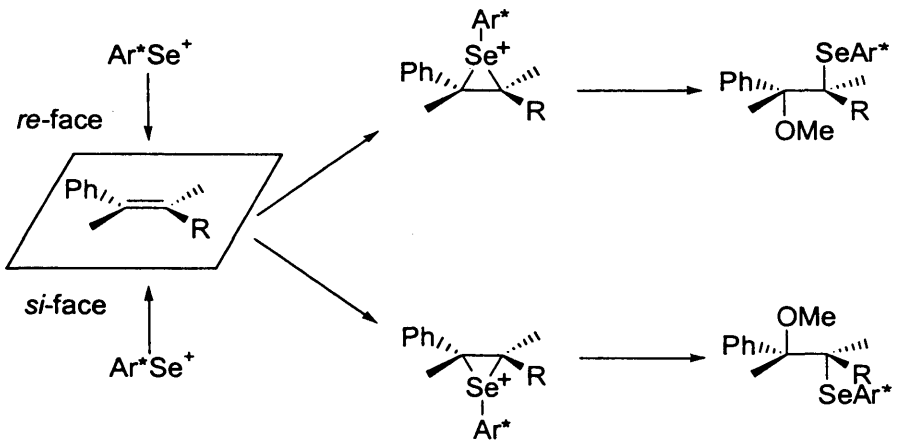


Figure 1-20 Origin of diastereomers during electrophilic attack

The highest selectivity obtained in these reactions is 98% *de*. A comparison of the performance of various chiral diselenides in the selenomethoxylation of styrene is given in Figure 1-25.

By using an alkene with an internal nucleophile, such as a carboxylic acid, alcohol or amino group, cyclisations are possible. Alkenes bearing an internal oxygen nucleophile have been found to give higher stereoselectivities than alkenes bearing an internal nitrogen nucleophile.

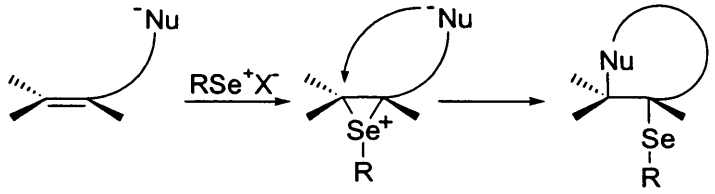


Figure 1-21 Selenocyclisations

The internal nucleophile can open the seleniranium cation by either *endo* or *exo* attack.

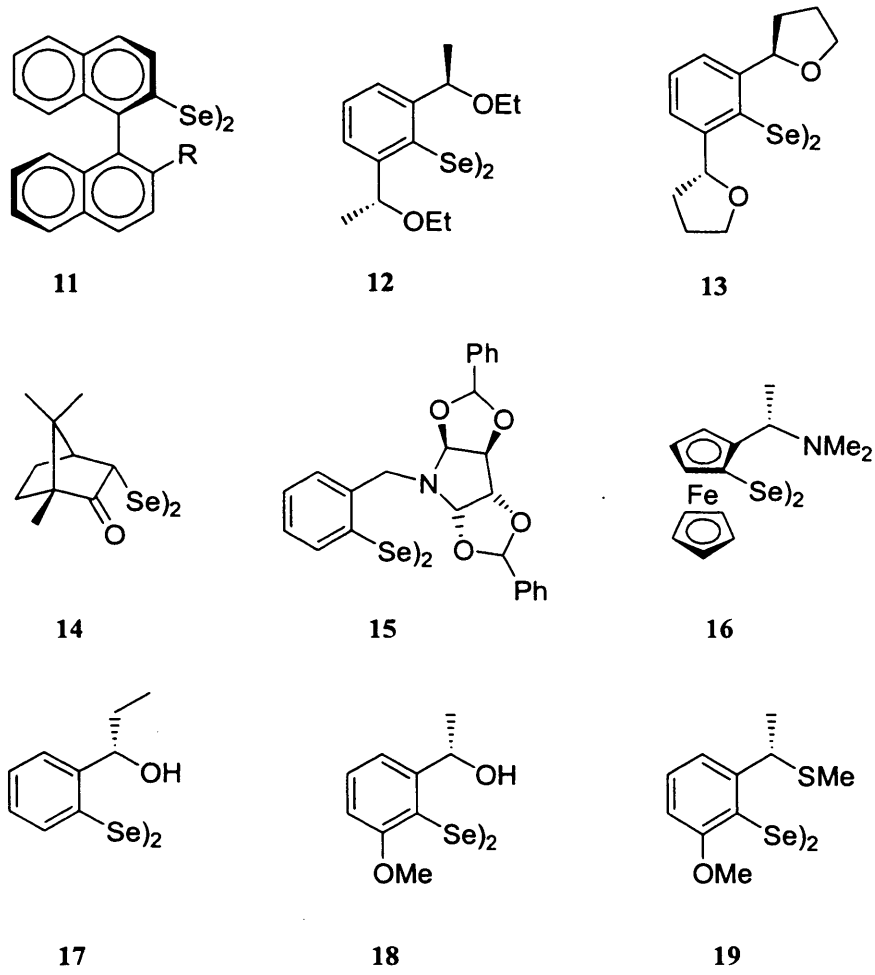


Figure 1-22 Selection of the more efficient chiral non-racemic diselenides

1.4 Diselenides as Catalysts[43]

A chemical one-pot reaction for the catalytic selenenylation deselenenylation of alkenes has been reported by Tiecco.[44] This method makes use of ammonium peroxydisulphate to generate an electrophilic selenium species **20** from diphenyl diselenide. Phenylselenenyl sulphate can attack the double bond of an alkene as previously described, in the presence of a nucleophile, to give the addition product **21**. The ammonium peroxydisulphate can then induce the elimination of the selenium moiety, regenerating the electrophilic species **20** and liberating the alkene **22**. The electrophilic selenium species can then react with the next alkene molecule. With only 10 mol% of diphenyl diselenide yields of up to 90% were achieved. It was found that the presence of an electron withdrawing group on the alkene was vital for the reaction to proceed in good yields.

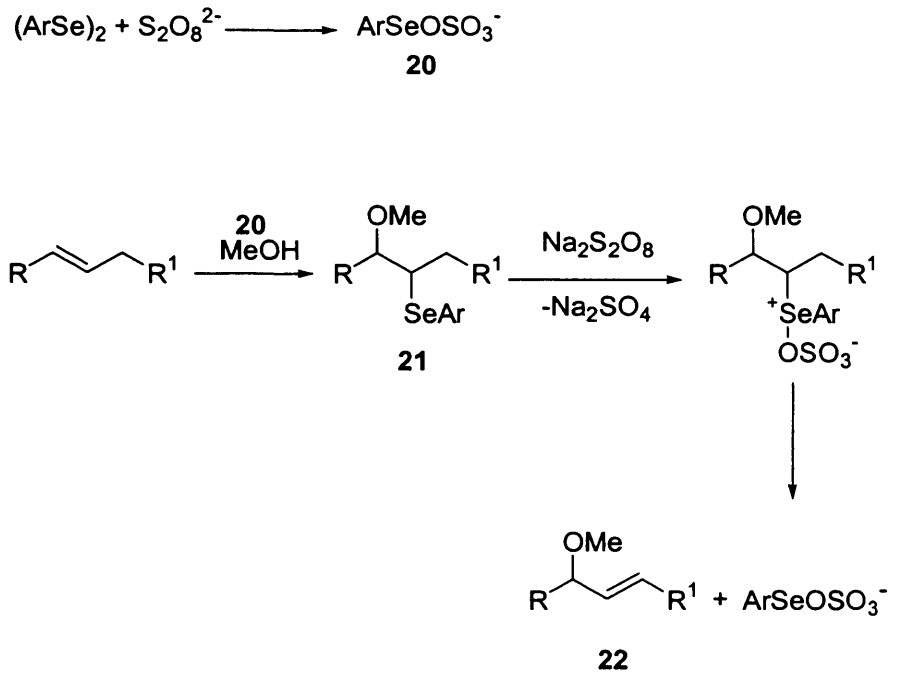


Figure 1-23 Catalytic use of diselenides using excess chemical oxidant

An alternative process for the catalytic use of diaryl diselenide for the allylic oxidation of alkenes has been described by Tomoda.[45] Using 10 mol% of diselenides bearing tertiary amines in the presence of copper (II) nitrate trihydrate with sodium persulphate as oxidant, yields of up to 59% were achieved. The reactive species in this system is believed to be a selenenic acid, and their investigation focussed on the stabilisation of this species.

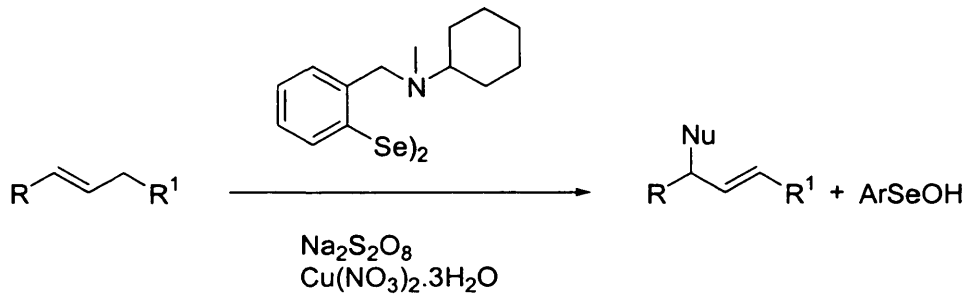


Figure 1-24 Catalytic use of diselenides via selenenic acid

These methods have been used by various groups to investigate the catalytic use of chiral diselenides for the asymmetric allylic oxidation of alkenes. Though yields remain generally low, selectivities of up to 75% *ee* have been achieved.[46] There are

two major drawbacks of this approach; the long reaction times required for the reaction to reach completion and the use of persulphate as the counter ion. Arylselenenyl sulphates are unreactive at temperatures below –30°C where most oxygen containing diselenides are most efficient. The low solubility in organic solvents of persulphate sources, typically sodium or ammonium persulphate, is deemed responsible for the low yields obtained when persulphate is used as the counterion.[30] A method that employs an oxidant which is effective at low temperatures and soluble in organic solvents would therefore seem desirable.

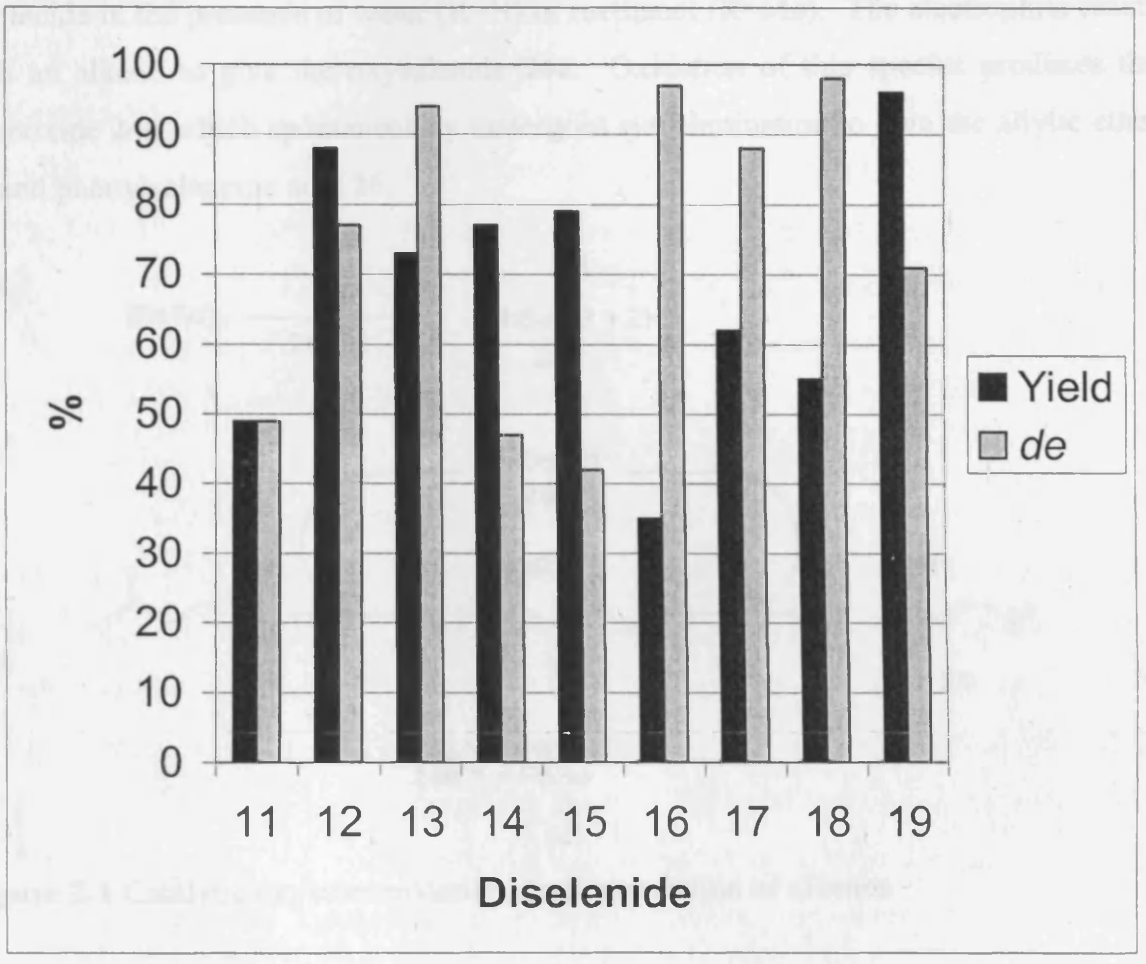


Figure 1-25 Comparison of efficiency of various diselenides for the selenomethoxylation of styrene at –78°C; **11** [26], **12** [47], **13** [31], **14** [48], **15** [49], **16** [50], **17** [51], **18** [52], **19** [53].

Chapter 2

Electrochemistry Results and Discussion

2.1 The Electrochemical Selenenylation-Deselenenylation of Alkenes

As shown by Torii *et al* the use of electrochemistry could enable the selenenylation and deselenenylation of alkenes to take place using a catalytic amount of diphenyl diselenide. The electrophilic species is **23**, generated by oxidation of diphenyl diselenide in the presence of water (R=H) or methanol (R=Me). The electrophile reacts with an alkene to give the oxyselenide **24a**. Oxidation of this species produces the selenoxide **24b** which spontaneously undergoes *syn* elimination to give the allylic ether **25** and phenylselenenic acid **26**.

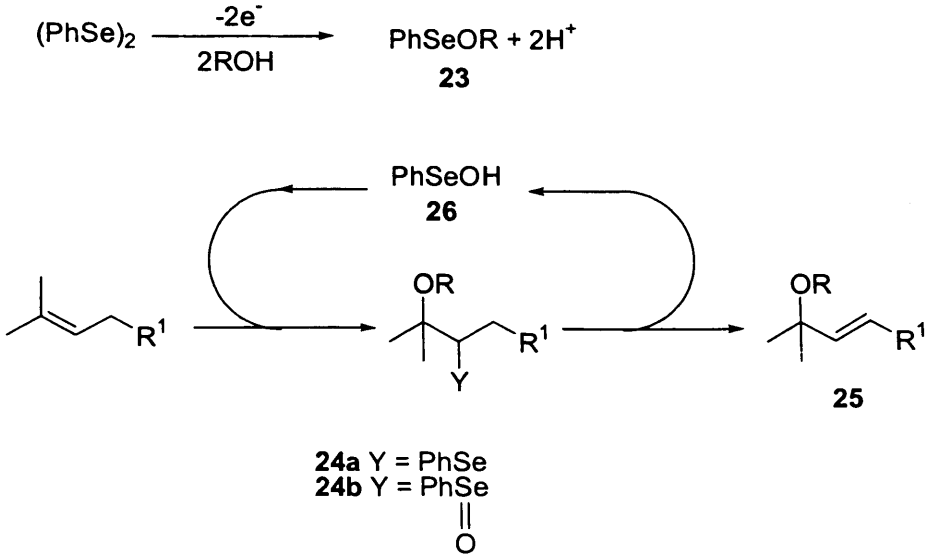


Figure 2-1 Catalytic oxyselenenylation deselenenylation of alkenes

A range of functionalities was found to tolerate this approach to double bond oxidation, including acetoxy, carbomethoxy, ethynyl and sulphonyl groups. Similar yields were obtained for methoxylation and hydroxylation reactions. In each of these reactions the electron efficiency was high, requiring between 3 and 5 F/mol for complete conversion depending on the substrate.

Of interest was the observation that using a stoichiometric amount of diphenyl diselenide required more electricity than the catalytic reaction. This is consistent with the fact that the eliminated species is at the correct oxidation state to add to the next molecule of alkene. For a perfectly electron efficient reaction, 2.2 F/mol would be required, based on 2 F/mol of diphenyl diselenide (0.2 eq. 2 electron oxidation to the electrophile **23**) and 2 F/mol of the alkene (1 eq. of the oxyselenide **24a** formed from the alkene undergoing a 2 electron oxidation to the selenoxide **24b**). The alkenes employed in the literature reactions ensured regioselectivity but did not result in the formation of allylic ethers possessing a chiral centre. Different alkenes were therefore required to investigate the electrochemical use of chiral diselenides.

2.2 Electrochemical Experimental Considerations

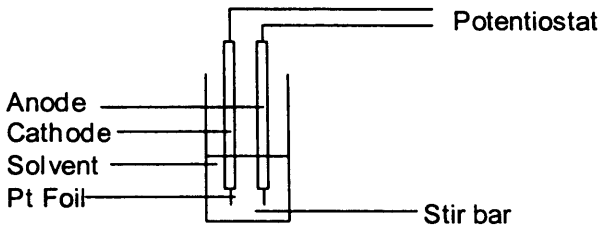
In order to carry out a successful investigation using synthetic electrochemistry, a certain level of background knowledge is required. The term electrochemistry covers a multitude of techniques and whilst familiarity with the bulk them is not essential, the synthetic electrochemist should have some grasp of the more fundamental aspects. A glossary of these aspects is found in appendix 1.

The style in which electrochemical investigations are reported in the literature varies considerably, with some authors describing in greater detail their experiments than other authors. In any report, the conditions such as the electrode material/type, solvent, reagents and stoichiometry are described. The disparity concerns the detail of the electrochemical aspect. Whilst describing the current that was passed during the experiment, or at the very least the rate of current flow and the time of the experiment, the potential that was required to achieve this current is not always given. In providing this information about the current, the author is indirectly providing the stoichiometry of the reaction in terms of the number of electrons "added" to the reaction. The number of electrons can be expressed in terms of a Faraday, where one Faraday is equal to the charge on one mole of electrons. The relationship between the current and the stoichiometry is calculated by the following equation:

$$\frac{\text{Reaction time (seconds)} \times \text{Current (milli-Amps)}}{\text{96484 C (the charge on a mole of electrons)}} = nF$$

The value F/mol is simply the above equation divided by the number of moles of the substrate used in the reaction.

The factor that determines the potential required to achieve a given current is the resistance of the cell. The resistance of the cell is normally reduced by the use of a suitable electrolyte which acts by carrying the electrical charge through the solution from one electrode to another as an ionic charge. The distance between the electrodes is directly related to the resistance, so as the distance between the electrodes increases so does the resistance. Given that the cell potential is critical in determining whether reactions can occur or not, it can been seen that both these variables, that is the concentration of the electrolyte and the distance between the electrodes, are important to an experimenter reproducing the conditions. The electrolyte concentration is always given when an electrochemical experiment is described. The distance between the electrodes is, however, frequently omitted. The overall potential of the cell is also frequently omitted and this can lead to problems when repeating a literature experiment. The type of cell chosen for this investigation was a simple undivided cell, as shown in the diagram below.



For the investigation into the electrochemical use of chiral diselenides, choice of substrate would influence the outcome of the reaction considerably. While the non-electrochemical elimination step where the oxidant is present in large excess results in facile elimination, the electrochemical elimination could have been more difficult. A substrate was therefore required which possessed an extra driving force for this elimination but was also known as an ideal substrate for regio- and stereoselective selenomethoxylation. Methylstyryl acetate **27** promised to fulfil these requirements, with the labile nature of the proton α to the carbonyl providing an extra driving force for the elimination step. Previous workers had shown that this compound could be

successfully selenomethoxylated with relatively high selectivity.[29] Accordingly, the non-electrochemical synthesis of **28** was carried out using phenyl selenenyl triflate followed by elimination to **30** using ammonium peroxydisulphate. This enabled the isolation and characterisation of the key compounds in the reaction sequence by GC-MS, making it possible for the electrochemical reaction to be followed in some detail.

Non-electrochemical selenenylation reactions are normally carried out in diethyl ether or sometimes THF. Electrochemical reactions require solvents with relatively high dipole moments, hence THF and ether are unsuitable. The procedures described in the literature make use of a mixture of acetonitrile and water for selenohydroxylations and pure methanol for selenomethoxylations. Methanol was chosen initially, distilled from magnesium and iodine before being degassed with argon prior to use.

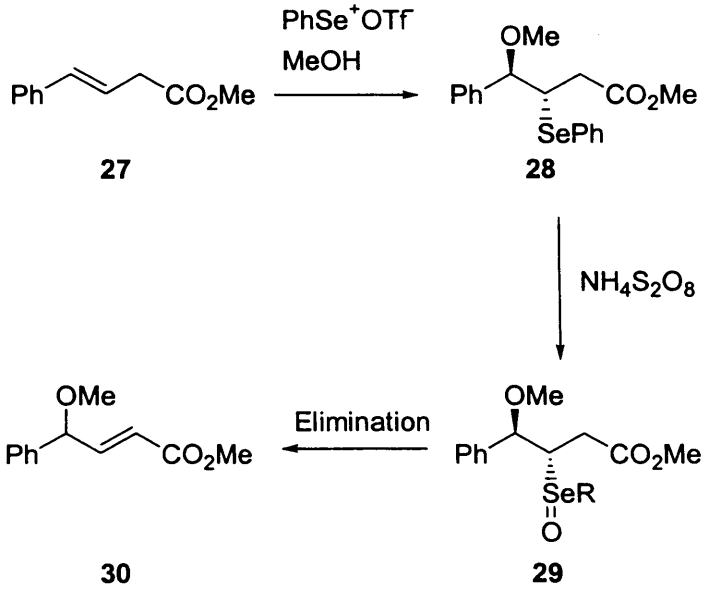


Figure 2-2 Traditional selenomethoxylation-demethoxylation sequence

Correct choice of electrode type/material is crucial in planning any electrochemical investigation. There are a number of options available to the electrochemist, ranging from foils or disks of metals to graphite sticks. The requirement here was for a low-cost electrode that would not react with carbon-carbon double bonds. Platinum foil electrodes, widely available and inert to alkenes, meet these requirements. To complete the apparatus a reference electrode was required. To begin with, a pseudo reference

electrode (consisting of a silver wire) was used to complete the circuit, although clearly incapable of providing information as to the potential of the cell.

The scale at which an electrochemical reaction can be successfully carried out is chiefly determined by the surface area of the electrodes. If a reaction is attempted on too large a scale for the size of the electrodes, complications arise as a result of increased reaction times.

2.3 Stoichiometric use of Diphenyl Diselenide

The first electrochemical reaction was carried out using 0.5 equivalents of diphenyl diselenide (effectively one equivalent of electrophile). In an attempt to emulate the conditions used by Torii for his catalytic sequence, no electron mediator was used. The aim was to directly oxidise diphenyl diselenide to the electrophilic species **23** which would then attack the alkene.

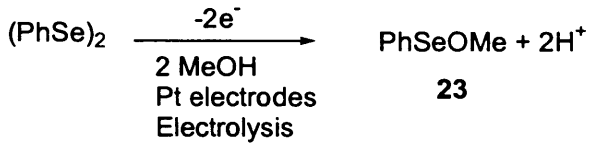
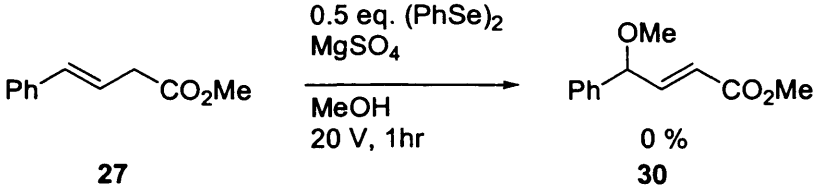


Figure 2-3 The direct electrochemical generation of the selenium electrophile

It was found that the conditions used by Torii would be difficult to reproduce. The primary difficulty was the potential required to provide the necessary current flowing through the cell. Only by increasing the potential to around 20 V was a suitable current attained. Working at such high voltages presents a number of problems, chiefly the substantial increase in the number of side reactions occurring. After an hour of electrolysis, the reaction mixture contained a large number of unwanted side products with virtually all of the alkene **27** consumed. A careful examination of the experimental set-up described by Torii failed to reveal any significant differences between the system used here and his.



27 **30**

Figure 2-4 Initial experimental conditions

Practical considerations were then taken into account, such as the stirring of the reaction. Repeating this reaction using more vigorous stirring had no effect, nor did using 'wet' methanol in the reaction. One substrate successfully used by Torii was β-citronellol, so this was used in place of **27**. Again, although the starting material was rapidly consumed at high voltages, the desired product was not formed.

The problem seemed to be the high electrical resistance of the cell. This could be overcome by the use of a suitable electrolyte. In Torii's earlier non-catalytic examples, tetraethyl ammonium bromide (TEAB) had been used as an electron mediator, the bromide being oxidised at the anode to bromine, the bromine itself then oxidising diphenyl diselenide to phenylselenyl bromide. TEAB is also readily soluble in methanol and hence could act as both the mediator and as the electrolyte.

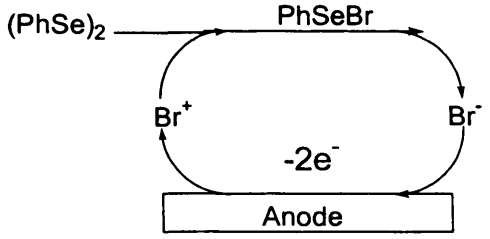
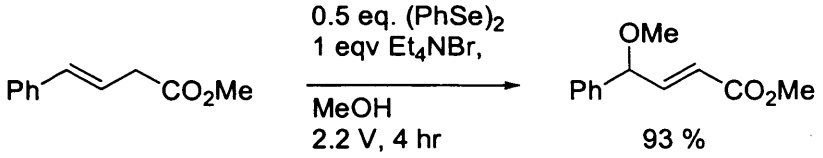


Figure 2-5 Bromide as an electron mediator

Using TEAB, the necessary current flow was achieved at a much lower cell potential than without TEAB. The reaction proceeded smoothly and the product **30** was isolated in high yield.



27 **30**

Figure 2-6 Stoichiometric use of $(PhSe)_2$

An observation that Torii had made was that trace amounts of sulphuric acid could prevent the elimination step taking place, and therefore enable isolation of the intermediate **28**. However, when a drop of sulphuric was added at the start of this reaction the elimination step proceeded as normal. The only effect observed in this system was the slight increase in the rate of the reaction. Though the presence of the intermediate **28** could be detected by GC-MS, the amount present at any given time was too low to consider isolation.

Table 2-1 Conversion of **27** into **30** using a stoichiometric amount of the electrophile

Potential	Current	Time	Acid	TEAB	Yield
22 V	2.2 mA	1 hr	None	None	0%
20 V	2.1 mA	40 hrs	None	None	Trace
4 V	2.6 mA	8 hrs	None	0.5 eq.	71%
2.5 V	2.0 mA	6 hrs	H_2SO_4	1.0 eq.	91%

Conditions: 0.2 mmol alkene and 0.1 mmol $(PhSe)_2$ in 7 ml methanol at room temperature, isolated yields given

2.4 Catalytic use of Diphenyl Diselenide

Having established conditions for the stoichiometric use of diphenyl diselenide, the amount of diselenide was reduced to 10 mol% of the alkene. Using the conditions described by Torii in his catalytic cycle, the same problems again were encountered, with a multitude of side products forming. Reverting to the conditions that proved ideal for the stoichiometric addition resulted in some product forming (Table 2-2). Here, the inclusion of trace amounts of sulphuric acid was to prove critical in boosting the yield. In the absence of any sulphuric acid, yields never exceeded 35%.

In the presence of sulphuric acid, the yield was 91%. This dramatic effect on the yield had no literature precedent and in some respects was counter intuitive (when consideration is given to the requirement for the presence of a negatively charged nucleophile).

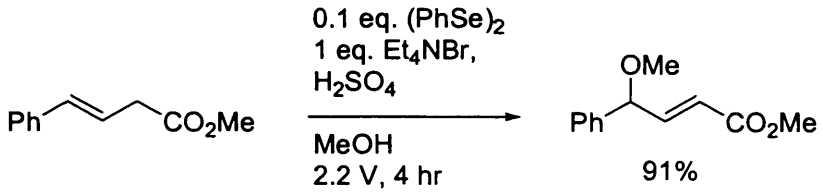


Figure 2-7 Optimum conditions for the conversion of **27** into **30** using 0.2 mmol alkene and 0.02 mmol $(PhSe)_2$ in 7 ml methanol at room temperature

It is believed that the acid is behaving as the ultimate electrolyte, reducing the resistance of the cell and enabling more current to flow at a given cell potential. However, this does not account for the differing observations from these experiments to those of Torii, where selenoxidation is suppressed.

Torii also described the use of certain inorganic salts in the reaction, ostensibly to prevent the overoxidation of the eliminated selenium species, phenyl selenenic acid **26** to the inert phenyl seleninic acid **26b**. The effect on this reaction with the inclusion of various salts is given in Table 2-2.

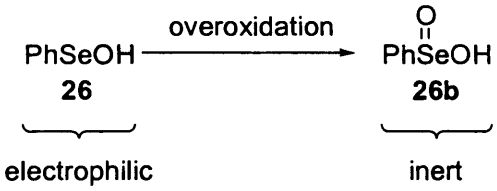


Figure 2-8 Overoxidation of the eliminated selenium species into unreactive seleninic acid

These inorganic salts appear to play no part in the catalytic cycle here, having merely a physical effect on the electrodes, coating them with a film of salt. Vigorous stirring overcomes this detrimental effect. It was rapidly becoming clear that there were large differences in the reaction described by Torii and the reaction here. An investigation

into the mechanism would clearly be required. Further reactions were now carried out to enable a fuller picture of these differences to emerge.

The effect of temperature on the reaction was also investigated due to the significant effect temperature has on reactions involving chiral selenium electrophiles. In the electrochemical reaction, at 21°C other factors appeared to be more significant. As the temperature was reduced to 0°C the yield was noticeably reduced even with the reaction times extended.

The use of additional electrolytes was also investigated. These would reduce the resistance of the cell still further, potentially preventing any side reactions from occurring. There are a large number of electrolytes available, some of which were however, too nucleophilic to be considered for use in this reaction. Tetraethylammonium was the ideal cation for the electrolyte, inert and highly soluble in organic solvents. Halide anions have the potential to act as nucleophiles or even, after anodic oxidation, electrophiles. This could increase the number of side reactions taking place and impact on the yield.

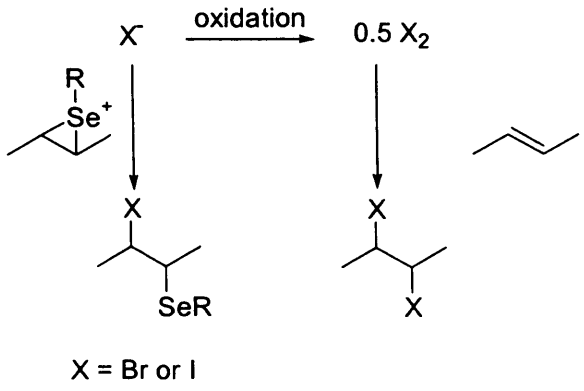
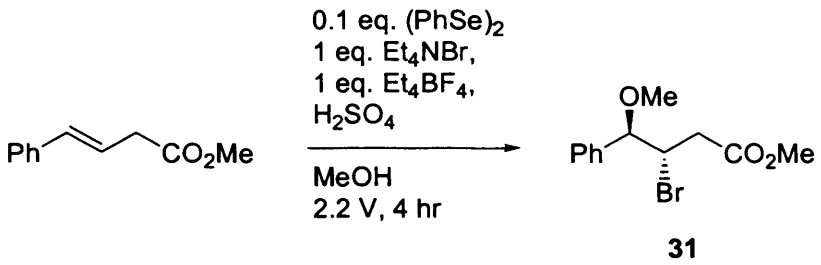


Figure 2-9 Side reactions involving halides

Hexafluorophosphate and tetrafluoroborate were therefore chosen as electrolytes. The number of side reactions that were able to occur with the use of these salts dramatically increased with the subsequent decrease in yield. Reaction between electrochemically generated bromine and the alkene now seemed to be occurring, with formation of bromoether **31** as the main product in yields of up to 63%.



31

Figure 2-10- Formation of the bromoether

Other acids were investigated in this reaction, including acetic acid. While the use of acetic acid in place of sulphuric acid had a small negative effect on the yield, hydrochloric acid had no effect on the reaction. This observation supports the idea that the role of the acid is merely as an electrolyte, as the different structures of hydrochloric and sulphuric acid might be expected to influence the course of the reaction differently if they were involved chemically rather than physically. Having investigated these factors, the optimisation of the non-asymmetric catalytic selenomethoxylation-deselenylation had been achieved and the project now moved onto investigations using chiral diselenides in place of diphenyl diselenide.

Table 2-2 Conversion of **27** into **30** using a catalytic amount of electrophile

Potential	Current	TEAB	Acid	Salt	Electrolyte	Temp	Time	Yield of **30**
4 V	2.1 mA	1 eq.	None	None	None	RT	8 hrs	5%
3.5 V	2.2 mA	1 eq.	None	$MgSO_4$	None	RT	6 hrs	Trace
3.2 V	2.1 mA	0.5 eq.	None	$CaSO_4$	None	RT	8 hrs	0%
2.2 V	4.0 mA	4 eq.	None	None	None	RT	8 hrs	Trace
5 V	2.2 mA	0.5 eq.	H_2SO_4	None	None	RT	8 hrs	**82%**
3.2 V	1.8 mA	None	None	None	Et_4NBF_4	RT	8 hrs	0%
3.0 V	2.4 mA	None	H_2SO_4	None	Et_4NBF_4	RT	8 hrs	0%
2.8 V	2.1 mA	0.5 eq.	H_2SO_4	None	Et_4NPF_6	RT	7 hrs	0%
2.9 V	2.2 mA	1 eq.	HOAc	None	None	RT	8 hrs	61%
3.1 V	2.5 mA	1 eq.	HCl	None	None	RT	7 hrs	**84%**
3.1 V	2.6 mA	1 eq.	H_2SO_4	None	None	RT	8 hrs	**91%**
2.9 V	2.3 mA	1 eq.	H_2SO_4	None	None	0°C	8 hrs	35%
2.8 V	2.1 mA	1 eq.	H_2SO_4	None	None	0°C	20 hrs	44%

Conditions: 0.1 mmol alkene, 0.01 mmol $(PhSe)_2$ in 7 ml methanol, yields from GC-MS (naphthalene as internal standard) except those given in bold type.

2.5 Electrochemical use of Chiral Diselenides

A number of chiral diselenides were available for this project having been synthesised previously within the group by standard methods.[54] For the initial experiments the chiral diselenides were to be used in stoichiometric amounts to establish their stability in electrochemical conditions, before investigating their potential as catalysts.

Diselenide **32** (Figure 2-12) was the first to be used in this reaction. Substitution of diphenyl diselenide with chiral diselenide **32** in the electrochemical reaction with alkene **27**, led to the formation of allylic ether **30** in the significantly reduced yield of 38%, with a large number of previously unobserved side products forming.

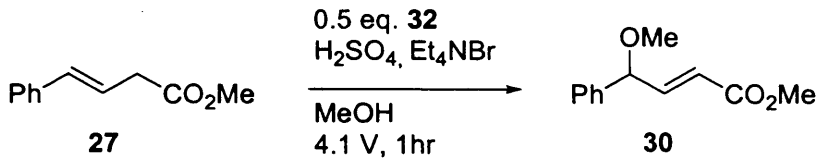
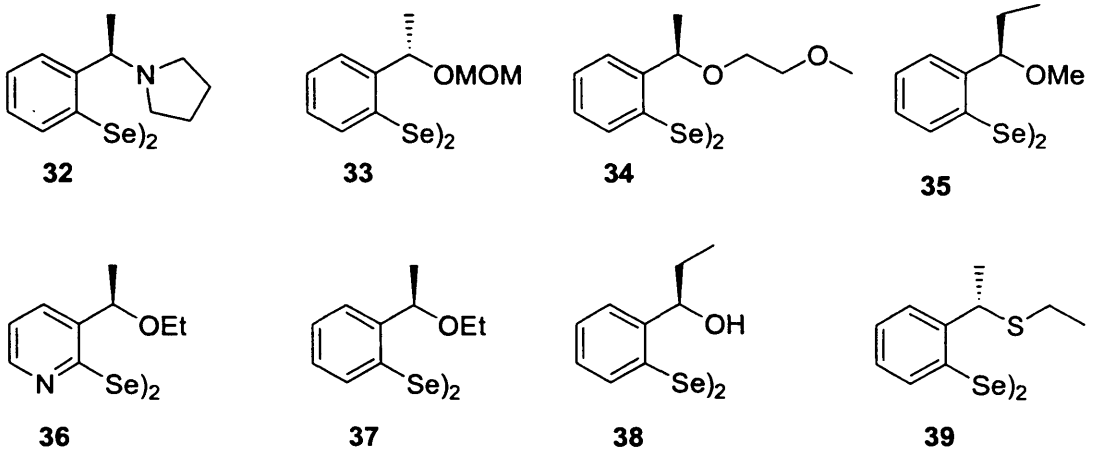


Figure 2-11 The first electrochemical reaction with a chiral diselenide

The low yield obtained here indicated that the reaction conditions would need to be varied from those that proved ideal for the use of diphenyl diselenide. Side reactions may have been caused by reaction of the pyrrolidyl moiety, or possibly by an increase in the oxidation potential of the diselenide. The reaction would be revisited at a later stage in an attempt to address this problem.



32 **33** **34** **35**

36 **37** **38** **39**

Figure 2-12 Chiral diselenides used in the electrochemical reaction

The next chiral diselenide employed for the conversion **27** into **30** was **33**. This diselenide can be synthesised in just two steps from commercially available starting materials and is proven to be an efficient reagent. When used in stoichiometric amounts the yield was again lower than had been obtained using diphenyl diselenide.

Five further chiral diselenides were used in these conditions and the results are given in Table 2-3. In none of the reactions was the diselenide detected at the end of the reaction.

Table 2-3 Results from the use of various chiral diselenides

Diselenide	Yield of **30**	*ee*
32	46%	0%
33	38%	3%
34	59%	7%
35	68%	15%

Conditions: (0.05 mmol) diselenide in the electrochemical selenenation-deselenenylation reaction with alkene **27** (0.1 mmol) in methanol (7 ml) using TEAB (0.1 mmol) and H_2SO_4 at a constant current of 2 mA, isolated yields given.

Having established that the electrochemical reaction of chiral diselenides with alkenes was possible, the use of these and other reagents in catalytic amounts was now investigated. The results are given in Table 2-4a.

Table 2-4a Catalytic use of chiral diselenides in the electrochemical reaction

Diselenide	Yield of **30**	*ee*
32	38%	0%
33	25%	0%
34	47%	3%
35	52%	17%
36	30%	31%
37	55%	5%
38	19%	44%
39	40%	69%

Conditions: (0.01 mmol) diselenide in the electrochemical selenenation-deselenenylation reaction with alkene **27** (0.1 mmol) in methanol (7 ml) using TEAB (0.1 mmol) and H_2SO_4 at a constant current of 2 mA, yields from GC-MS (naphthlene as internal standard).

Of interest is the similarity in the yields for a given diselenide whether the diselenide is used in a stoichiometric or catalytic amount. This indicates that all of the allylic ether **30** that forms is as a result of reaction with the electrochemically generated selenium electrophile rather than by an alternative pathway.

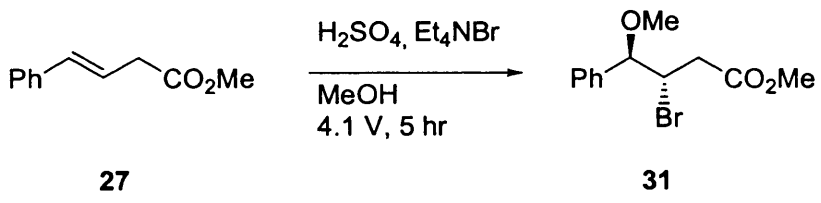
The reaction of diselenide **33** with alkene **27** was investigated in detail, with close attention paid to the side reactions that occurred. The results of this process of optimisation are given in Table 2-5. The enantiomeric excess of the product **30** remained at 0% in all conditions.

Table 2-4b Optimisation of the use of chiral diselenide **33**

Potential	F/mol	TEAB	Acid	Salt	Electrolyte	Time	Yield of **30**
3.9 V	5.9	1 eq.	H_2SO_4	None	None	8 hrs	25%
4.4 V	5.9	1 eq.	None	None	None	8 hrs	35%
3.8 V	5.2	2 eq.	None	None	None	7 hrs	**41%**
3.5 V	5.2	5 eq.	None	None	None	7 hrs	31%
3.7 V	5.9	2 eq.	None	None	Et_4NPF_6	8 hrs	35%
4.1 V	3.7	None	None	None	Et_4NPF_6	5 hrs	0%
3.9 V	5.2	2 eq.	H_2SO_4	None	None	7 hrs	28%
4.2 V	5.9	2 eq.	None	$MgSO_4$	None	8 hrs	39%
3.9 V	7.4	3 eq.	None	None	None	10 hrs	**62%**
3.9 V	10.4	3 eq.	None	None	None	14 hrs	**60%**

Conditions: diselenide (0.01 mmol) in the reaction with alkene **27** (0.1 mmol) in 7 ml methanol at room temperature and at 2 mA constant current, yields from GC-MS (naphthlene as internal standard).

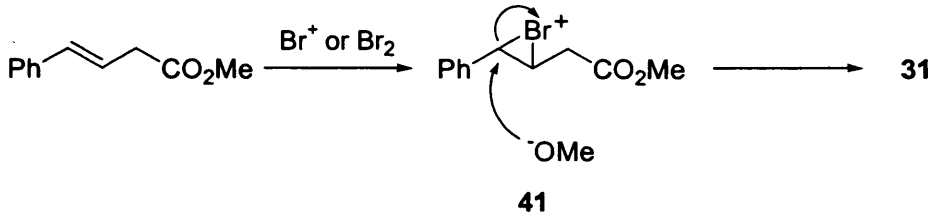
As the concentration of TEAB was increased the amount of a particular side product also increased. The reaction was repeated in the absence of any diselenide allowing this product to form in 70% yield. This product, formed as a single diastereomer, was identified as **31**.



27 **31**

Figure 2-13 Reaction in the absence of diselenide using dry methanol

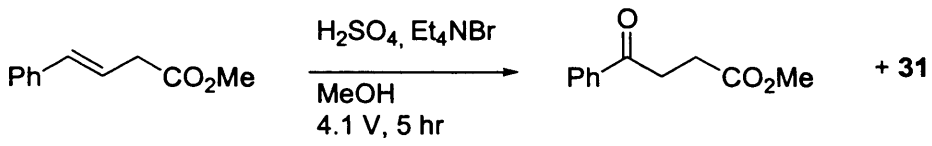
This compound appears to form either as a result of the direct attack of the double bond by Br^+ or by the attack of bromine, to form the intermediate **41**. This bromonium ion is opened by methanol to give the bromoether **31**. The *anti* stereochemistry is assigned by consideration of the transition state.



41

Figure 2-14 Formation and reaction of bromonium ion

Interestingly, when methanol that had not been dried and degassed was employed, the major product was ketone **42** which formed in differing yields up to 40% as the conditions were varied. When water was added to the reaction, the ketone formed in 63% yield. The non-electrochemical equivalent of this transformation is the Wacker reaction, where palladium is used as the oxidant. Whilst an electrochemical version of the Wacker reaction has been reported, the direct electrochemical conversion of alkenes into ketones in the absence of palladium is unknown.[55] This was not investigated further but remains of interest.



42

Figure 2-15 Reaction in the absence of diselenide using undried methanol

As the amount of TEAB in the reaction is increased, the amount of bromoether **31** forming also increases. Given the reliance of the overall reaction on the presence of TEAB as a redox catalyst, this side reaction presents a problem. Tables 2-2 and 2-4 show the failure so far of the reaction to work without TEAB. A series of experiments was now carried out to directly establish the scope for reactions without the use of TEAB (Table 2-5). In all of these reactions the yield was less than 5% by GC-MS and therefore the product was not isolated or analysed by chiral HPLC.

The first reactions involved a straight swap of TEAB for tetraethylammonium tetrafluoroborate (entries 1-6). The aim of this was to allow the direct oxidation of the diselenide to the electrophilic species **43** whilst keeping the cell potential low enough to prevent direct oxidation of the double bond electrochemically. The effects of sulphuric and hydrochloric acids were also investigated. The cell potential was also varied to ensure that the oxidation potential of the diselenide would be reached.

$$(Ar^*Se)_2 \xrightarrow{-2e^-,\ 2\ MeOH} \underset{\mathbf{43}}{2\ Ar^*SeOMe}$$

Figure 2-16 Direct oxidation of diaryl diselenide to an electrophilic species

Table 2-5 Conversion of **27** into **30** using 10 mol% of diselenide **33**

Entry	Voltage	Current	F/mol	Acid	Salt	Electrolyte	Time
1	3.1 V	2 mA	5.97	H_2SO_4	None	Et_4NBF_4	8 hrs
2	3.9 V	2 mA	5.97	HCl	None	Et_4NBF_4	8 hrs
3	5.8 V	5 mA	14.92	H_2SO_4	None	Et_4NBF_4	8 hrs
4	16.4 V	10 mA	14.92	H_2SO_4	None	Et_4NBF_4	4 hrs
5	3.8 V	2 mA	5.97	None	None	Et_4NBF_4	8 hrs
6	6.4 V	4 mA	11.94	None	None	Et_4NBF_4	8 hrs
7	4.2 V	2 mA	5.97	None	None	Et_4NPF_6	8 hrs
8	5.5 V	5 mA	14.92	H_2SO_4	None	Et_4NPF_6	8 hrs
9	4.8 V	1 mA	6.72	None	$MgSO_4$	None	18 hrs
10	3.5 V	2 mA	5.97	H_2SO_4	$MgSO_4$	None	8 hrs
11	5.7 V	5 mA	14.92	H_2SO_4	$MgSO_4$	None	8 hrs
12	9.1 V	10 mA	14.92	H_2SO_4	$MgSO_4$	None	4 hrs
13	3.6 V	2 mA	5.97	None	$MgSO_4$	Et_4NBF_4	8 hrs
14	5.1 V	5 mA	14.92	H_2SO_4	$MgSO_4$	Et_4NBF_4	8 hrs
15	4.1 V	2 mA	5.97	None	$MgSO_4$	Et_4NPF_6	8 hrs
16	3.8 V	2 mA	7.46	H_2SO_4	$CaSO_4$	None	10 hrs
17	3.2 V	2 mA	5.97	HCl	$CaSO_4$	Et_4NBF_4	8 hrs
18	5.2 V	5 mA	16.79	H_2SO_4	$CaSO_4$	Et_4NPF_6	9 hrs
19	5.6 V	2 mA	7.46	None	$CaSO_4$	None	10 hrs

Conditions: diselenide (0.01 mmol) in the reaction with alkene **27** (0.1 mmol) in 7 ml methanol at room temperature and at 2 mA constant current.

Having determined that the electrochemical reaction with **33** with an alkene was critically dependant on a redox mediator, alternatives to bromide were now considered. A mediator was required that would not react with a carbon-carbon double bond. The results of these experiments are given in **Table 2.6**.

Table 2-6

Entry	Halide source	Equivalents	Yield of **30**
1	Et_4NI	1	0%
2	Et_4NI	2	0%
3	Et_4NCl	1	< 5%
4	Et_4NCl	2	< 5%
5	Bu_4NBr	1	48%
6	Bu_4NBr	2	58%
7	Et_4NBr	1	62%

Conditions: 0.01 mmol diselenide **33** with alkene **27** (0.1mmol) at 2 mA constant current in 7 ml dry methanol for 4 hours, yields from GC-MS (naphthalene as internal standard).

The trace of product that formed when chloride was used was not isolated and so the *ee* was not determined. The *ee* remained at 0% for entries 5-7. The main product from entries 1-4 was ketone **42** though not all of the alkene **27** was consumed after 4 hours. The conclusion was reached that the optimum conditions for the use of this particular diselenide had been found, giving a yield of 62%. It is noteworthy that in all of the experiments where a significant yield was obtained, the diselenide was not recovered or indeed detected in the crude reaction ^1H NMR spectra. This observation strongly supports the idea that the yield of the reaction is determined by the decomposition of the diselenide.

Consideration was now given to the stereoselectivity of the reaction. Table 2-3 illustrates the selectivities attained so far. The generally low selectivities observed in these reactions are attributed to the temperature at which these experiments were carried out. These oxygen diselenides have been optimised for use at low temperatures, at which they perform efficiently.[40] (Figure 1-25). The optimised electrochemical reaction

of **33** was now tried at a range of temperatures (Table 2-7). The failure of the reactions to work below 0°C was unexpected, as the alkene reacts with phenylselenenyl bromide at low temperatures in the non-electrochemical reaction. This lack of reactivity at low temperatures remains unresolved.

Novel diselenide **39** was synthesised for this project after a recent paper demonstrating that sulphur diselenides perform more efficiently than oxygen containing diselenides at room temperature.[54] The relatively high selectivity obtained by the use of sulphur based diselenide **39** was consistent with observations made in non-electrochemical reactions.

Table 2-7 Effect of temperature on the reaction of alkene **27** with various diselenides

Entry	Diselenide	Temperature	Yield	*Ee*
1	**33**	20°C	62%	0%
2	**33**	0°C	18%	0%
3	**33**	-30°C	0%	-
4	**35**	20°C	62%	17%
5	**35**	0°C	24%	21%
6	**35**	-30°C	0%	-
7	**38**	20°C	19%	44%
8	**38**	0°C	8%	43%
9	**38**	-10°C	Trace	N/d
10	**38**	-20°C	0%	-

Conditions: (0.1 mmol) with various diselenides (0.01 mmol) in methanol (7 ml), TEAB (0.1 mmol) and H_2SO_4, yields from GC-MS (naphthalene as internal standard).

2.6 Cyclic Voltammetry Experiments

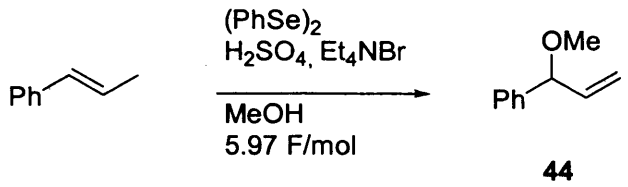
Cyclic voltammetry experiments were carried out on alkene **27**, diphenyl diselenide and chiral diselenide **33**. As the reactions were being carried out in methanol, the initial CV experiments were also carried out in methanol, using a silver/silver nitrate 0.01 M reference electrode and tetraethylammonium tetrafluoroborate as the supporting electrolyte. These initial experiments were unsuccessful in establishing the oxidation

potentials due to the poor quality of the voltammograms. When acetonitrile was used as the solvent the quality of the voltammograms improved and several illuminating results were obtained. In these conditions the alkene was found to have an irreversible oxidation at a potential of +1.65 V compared to ferrocene. Diphenyl diselenide gave an irreversible oxidation at a potential of 0.99 V compared to ferrocene. Chiral diselenide **33** gave an irreversible oxidation at a potential of 1.32 V compared to ferrocene. This clearly indicates that it is in principle possible to directly oxidise the diselenides to an electrophilic species without directly oxidising the alkene. The difference in oxidation potential between diphenyl diselenide and the chiral diselenide may account for the difference in reactivity towards the alkene. The larger difference between diphenyl diselenide and alkene **27** (0.66 V) than between chiral diselenide **33** and alkene **27** (0.35 V) should be easier to exploit when optimising the conditions. These results must be treated with caution however, taking into account the different solvents involved in the measurement experiment and the preparative reaction. The values obtained, whilst useful for direct comparison purposes, cannot be considered absolute values to be used in setting up the preparative reaction, primarily because of the difference in the presence/concentration of the supporting electrolyte. Cyclic voltammograms were not obtained for the full range of chiral diselenides and alkenes employed due to restricted access to the necessary equipment.

2.7 Alternative Substrates

In all of these reactions a significant amount of unreacted starting material was recovered. The reaction was stopped when the concentration of the product remained constant. Alternative substrates were now considered in the hope that these alkenes would prove more stable than **27**. The standard test reaction for new chiral diselenides is the selenomethoxylation of styrene. The product of this addition cannot however undergo selenoxide elimination and so could not be used in this system.

β-Methyl styrene was chosen as the next substrate. The electrochemical conversion of β-methyl styrene into allylic ether **44** with diphenyl diselenide was investigated.



44

Figure 2-17 Reaction of methyl styrene with diphenyl diselenide in methanol (7 ml) at 2 mA for 8 hrs

From the first experiment the number of side reactions was significant. Even when a stoichiometric amount of diphenyl diselenide was employed the yield of these reactions remained low. The main side product from these reactions was diether **45**. This diether formed in generally good yields, although it was not the exclusive product. The dibromo adduct **46** was detected in small amounts as was the ketone **47**.

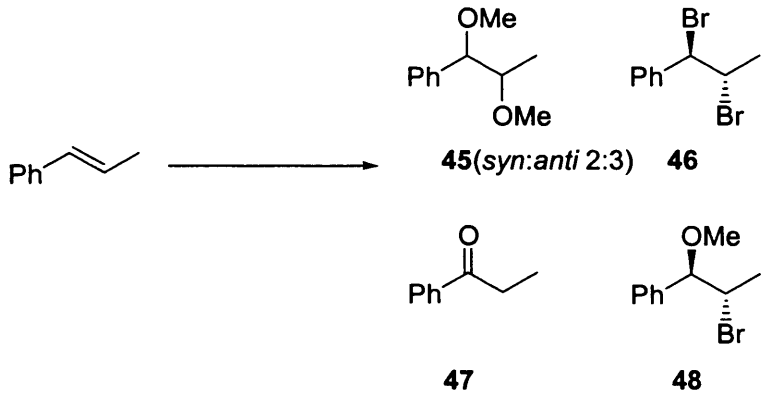


Figure 2-18 Products formed following electrolysis of β-methylstyrene with diphenyl diselenide in methanol using various conditions

The second most abundant side product was an analogue of one observed from the electrochemical reaction involving **27**. This bromo-ether **48** formed in good yields when TEAB was used. In the absence of TEAB, the main product was ketone **47**. When alternative electrolytes were used the main product was the diether **45**.

A search of the literature reveals that alkenes can react in a variety of different ways when subjected to electrolysis. It is well know that the alkenes can undergo coupling in methanol to give the 1-4 methoxy dimers.[56]

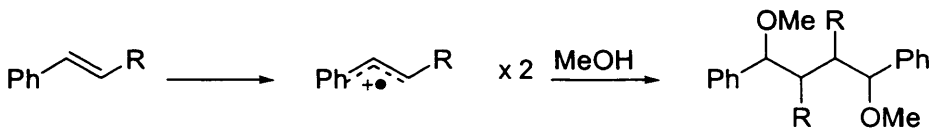
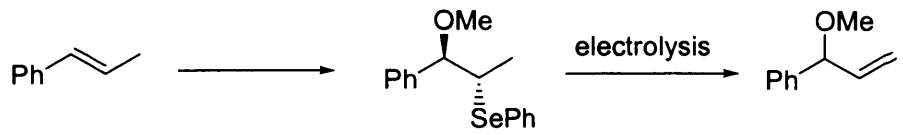


Figure 2-19 Electrochemical alkene dimerisation

However, β-alkyl substituents drastically decrease the yield of these dimers in favour of the dimethoxylated monomers.[57] This is clearly observed in the side products when β-methylstyrene and diphenyl diselenide are electrolysed in the presence of methanol. Whilst no coupling product is generated, the dimethoxy monomers **45** form in good yields (65% overall, *syn*:*anti* 2:3). This dimethoxylation reaction takes place in competition with the selenenylation reaction. When the electrolysis is performed in the absence of a diselenide or a bromide source, the diether **45** is the major product. When a bromide source is introduced, the formation of the bromonium ion occurs in competition with the diether formation. Predictably, as the concentration of the bromide source was increased, bromoether **48** was formed in preference to the diether **45**. When the concentration of bromide exceeded that of the alkene, the bromide addition product **48** was the exclusive product. Given the ease with which both of these side reactions occur, the low yields of the desired allylic ether **44** can be readily accounted for.

The addition product **49** was synthesised non-electrochemically and electrolysed in a range of conditions to obtain the elimination product **44**. This electrochemical elimination proved to be relatively high yielding (up to 70%), suggesting that the problem step in the sequence is the formation of **49**.



49 **44**

Figure 2-20 Electrochemical elimination step

The non-electrochemical synthesis of **49** with phenylselenenyl bromide takes place in reasonable yield (57%). This yield can be improved by the use of an alternative counter-ion, such as triflate. The non-electrochemical reaction of alkene **27** with phenylselenenyl bromide takes place in a higher yield than the corresponding reaction

with β-methylstyrene (83% compared to 57%), and this difference in reactivity appears to be reflected in the electrochemical reactions.

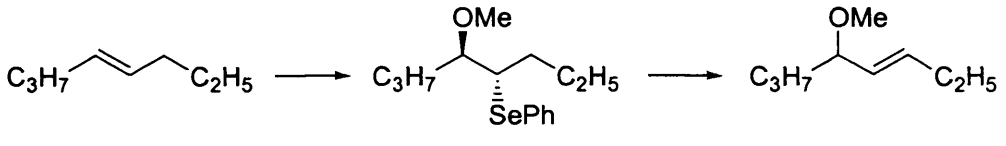
Table 2-8 Reaction between β-methylstyrene and diphenyl diselenide

Entry	$(PhSe)_2$	TEAB	Acid	Salt	Yield
1	0.5 eq.	1 eq.	H_2SO_4	None	33%
2	0.5 eq.	1 eq.	None	None	27%
3	0.5 eq.	0.5 eq.	None	None	18%
4	0.5 eq.	1 eq.	H_2SO_4	Et_4NBF_4	24%
5	0.5 eq.	1 eq.	H_2SO_4	Et_4NPF_6	19%
6	0.5 eq.	0.5 eq.	H_2SO_4	Et_4NBF_4	14%
7	0.5 eq.	None	H_2SO_4	Et_4NPF_6	Trace
8	0.5 eq.	none	H_2SO_4	Et_4NPF_6	Trace
9	0.1 eq.	TEAB	None	None	None
10	0.1 eq.	None	H_2SO_4	Et_4NBr	None

Conditions: diselenide (0.05 mmol), alkene (0.1 mmol) in methanol (7 ml) at 2 mA constant current, yields from GC-MS (naphthalene as internal standard).

Conditions for a high yield even when using a stoichiometric amount of diphenyl diselenide have yet to be found. The substrate alkene is too reactive to be successfully used in this reaction. A less reactive alkene was therefore required. *trans*-4-Octene was chosen and as before treated with phenyl selenenyl bromide in a non-electrochemical reaction to generate the intermediate compound **50**. This compound was treated with ammonium peroxydisulphate to give the elimination product **51**.

With these two compounds for reference, *trans*-4-octene was electrolysed in the presence of diphenyl diselenide. This proved to be a much cleaner reaction, with only a small amount of any side products forming.



50 **51**

Figure 2-21 Electrochemical reaction of *trans*-4-octene with diphenyl diselenide

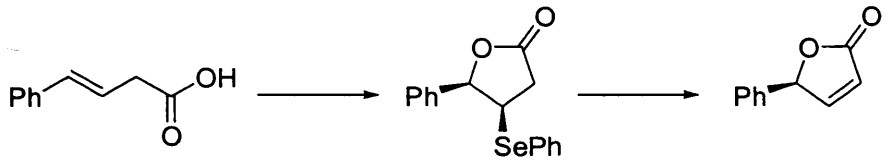
The yield however, remained relatively low. After 12 hours of electrolysis a large amount of the starting material remained. Further electrolysis failed to give more product, while the alkene was slowly consumed by the predicted side reactions leading to diether and bromoether formation. A trace of the product of a second addition and elimination of diphenyl diselenide to the alkene was also detected by GC-MS but in too low an amount to consider isolation. This observation was in some senses predicted as the constant regeneration of the electrophilic species, the basis of the catalytic cycle, was taking place without removal of the product, the product being an ideal substrate for a second reaction with the reagent. This had not been observed with the other substrates as this second elimination reaction step would not have been possible.

52

Figure 2-22 Second addition elimination sequence

The conditions for the reaction were varied considerably in an attempt to increase the yield. The highest yield obtained in this reaction was 36%. Given that this low yield was achieved using a stoichiometric amount of diselenide, the prospects for the catalytic reaction with this substrate were not promising. Attempts at this reaction with a catalytic amount of diphenyl diselenide did lead to some product forming, but in such low yields that it was not isolated. The low yields obtained using diphenyl diselenide precluded the use of chiral diselenides in the electrochemical reaction with this alkene.

As previously mentioned, when an alkene possesses an internal nucleophile reaction with a selenium electrophile can lead to the formation of a cyclic product. The acid **53** from which the ester **27** is derived was now employed as the substrate in the electrochemical selenenylation-deselenenylation sequence.



53 **54** **55**

Figure 2-23 Electrochemical selenolactonisation deselenenylation sequence

As before the intermediate **54** was synthesised by the standard non-electrochemical method in order to provide reference compounds for the reaction to be followed. Using a stoichiometric amount of diphenyl diselenide in acetonitrile with TEAB as electrolyte/redox mediator in a variety of conditions gave an optimised yield of 34% of cyclic alkene **55**. The catalytic use of diphenyl diselenide gave an optimised yield of 10%.

Table 2-9 Reaction between diphenyl diselenide and **53** to give **55**

Potential	F/mol	$(PhSe)_2$	TEAB	Acid	Electrolyte	Time	Yield
3.2 V	5.97	1 eq.	1 eq.	H_2SO_4	None	8 hrs	34%
3.8 V	5.97	1 eq.	1 eq.	None	None	8 hrs	18%
4.0 V	8.95	1 eq.	None	H_2SO_4	Et_4NBF_4	12 hrs	< 5%
5.5 V	8.95	1 eq.	None	None	Et_4NBF_4	12 hrs	Trace
2.8 V	5.97	1 eq.	3 eq.	H_2SO_4	None	8 hrs	23%
3.3 V	17.91	1 eq.	3 eq.	None	None	24 hrs	25%
3.3 V	5.97	0.2 eq.	1 eq.	H_2SO_4	None	8 hrs	< 5%
5.0 V	5.97	0.2 eq.	None	None	Et_4NBF_4	8 hrs	Trace
3.0 V	8.95	0.2 eq.	2 eq.	H_2SO_4	None	12 hrs	10%
7.6 V	17 .91	0.2 eq.	None	none	None	24 hrs	Trace

Conditions: Diphenyl diselenide with alkene **53** (0.1 mmol) in acetonitrile (7 ml) at room temperature, yields from GC-MS (naphthalene as internal standard).

Given the low yields in this reaction using diphenyl diselenide, the use of chiral diselenides was not investigated with this substrate.

2.8 Hydroxylation Reactions

The synthesis of allylic alcohols by the same electrochemical methodology as allylic ethers has been achieved by using an acetonitrile-water mixtures in place of methanol. A range of alkenes was converted to the corresponding allylic alcohols by electrolysis in the presence of diphenyl diselenide.

Several attempts at re-creating the conditions described in the literature were unsuccessful. As before, the cell potential required to generate the flow of current used by Torii lead to the rapid consumption of the starting material by a myriad of side reactions. Reverting back to the conditions used in the synthesis of allylic ether **30**, the product **56** could be formed in low yield (25%).

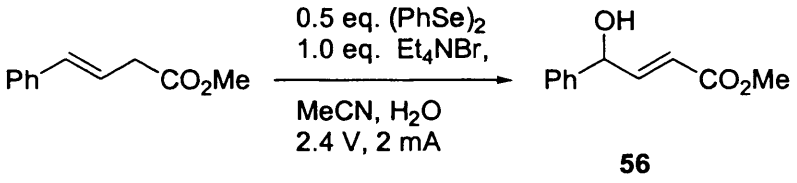


Figure 2-24 Electrochemical hydroxyselenenylation-deselenenylation reaction

The conditions were varied as previously to optimise the reaction (Table 2-10). As before, however, there were a number of side reactions occurring. The major, almost exclusive product from this reaction was the ketone **42**. The other products formed in too low a yield for their identification.

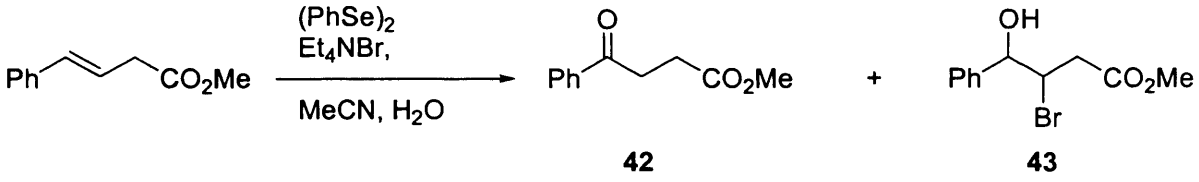


Figure 2-25 Formation of side products

Increasing the concentration of TEAB proved the most effective modification to these conditions. The major side product from this reaction was still the ketone **42**, although as the TEAB concentration increased still further a different side product formed, believed to be the bromohydrin **43** though this could not be isolated. Again, due to the

low yields obtained using diphenyl diselenide, the use of chiral diselenides was not thoroughly investigated. A small number of selenohydroxylations using chiral reagents **34, 37** and **38** were attempted but none of the desired allylic alcohol was formed.

Of the four alkenes that were investigated for the electrochemical selenenylation-deselenenylation reaction, cinnamic acid derivative **27** has given the most satisfactory results. The conditions required for the selenenation-deselenenylation of the other 3 alkenes proved unsuitable because of the side reactions these conditions facilitated.

Table 2-10 Optimisation of the reaction between diphenyl diselenide and alkene **27** to give **56**

Potential	Current	F/mol	TEAB	Acid	Electrolyte	Time	Yield
2.4 V	2 mA	5.97	1 eq.	H_2SO_4	None	8 hrs	25%
2.7 V	2 mA	5.97	0.1 eq.	H_2SO_4	None	8 hrs	< 5%
4.1 V	4 mA	8.95	1 eq.	H_2SO_4	None	6 hrs	31%
5.2 V	4 mA	8.95	0.1 eq.	None	None	6 hrs	< 5%
2.2 V	2 mA	5.97	3 eq.	None	None	8 hrs	36%
2.0 V	2 mA	5.97	4 eq.	None	None	8 hrs	30%
2.5 V	2 mA	5.97	1 eq.	H_2SO_4	Et_4NBF_4	8 hrs	27%
3.3 V	2 mA	5.97	1 eq.	None	None	8 hrs	18%
2.7 V	2 mA	14.92	1 eq.	None	None	20 hrs	29%
3.5 V	4 mA	5.97	1 eq.	H_2SO_4	Et_4NPF_6	4 hrs	23%
12 .0 V	8 mA	5.97	1 eq.	H_2SO_4	None	2 hrs	< 5%

Conditions: acetonitrile water mixture (7 ml) at a constant current, yields from GC-MS (naphthalene as internal standard).

2.9 Mechanism of the Methoxyselenenylation Deselenenylation Sequence

Torii proposed the following mechanism for the electrochemical catalytic sequence. The electrophile, formed in the absence of an electron mediator, is **23**. This electrophile adds to the alkene to form a seleniranium cation which is opened by methanol to give the intermediate **28a** as the exclusive regioisomer. Oxidation to the selenoxide **28b** occurs, though whether this is an electrode process or a homogeneous reaction is not

clear. The selenoxide undergoes elimination to produce the alkene **30** and selenenic acid **26**, itself an electrophile, which can react with the next equivalent of alkene.

There are two key features of this mechanism which are incompatible with the present investigation. Firstly, having failed to generate **23**, a redox mediator was employed to generate an electrophilic selenium species. Secondly, the oxidation step to form the selenoxide **29** requires a source of oxygen. The use of carefully dried and degassed solvent together with an inert atmosphere should therefore prevent the elimination step taking place. This is not what was observed. A series of experiments was now carried out in order to elucidate the mechanism for the electrochemical reaction of chiral diselenides with alkenes.

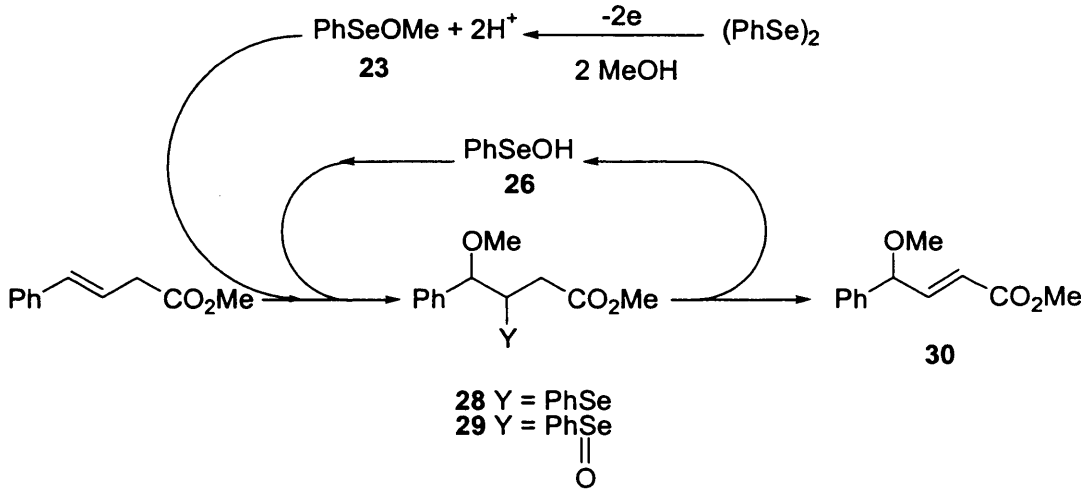


Figure 2-26 Mechanism for the catalytic electrochemical use of diphenyl diselenide as proposed by Torii

In following the reactions by GC-MS, the electrophilic species phenylselenenyl bromide had been observed. This electrophilic selenium species must be generated from the reaction of diphenyl diselenide with bromine generated at the anode by oxidation of two equivalents of bromide. Reaction of selenenyl bromide with the alkene produces the intermediate **28**, as confirmed by the non-electrochemical reaction (Figure 2-2).

In the absence of bromide, the electrophilic species **23** was not observed by GC-MS. Diphenyl diselenide was observed, and the use of an internal standard (naphthalene)

indicated that electrolysis of diphenyl diselenide in methanol in the presence of the alkene **27** did not lead to a reduction in the concentration of diphenyl diselenide. As the cell potential was increased, the diphenyl diselenide concentration was observed to decrease, along with the concentration of the alkene, as a range of side products began to form. At no point was there a trace of either the intermediate **28** of the target alkene **30**. In addition to using methylstyryl acteate **27** as the substrate, β-citronellol was also used. The conditions were as close to those successfully employed Torii as it was possible to create. Again, no reaction was observed until the cell potential was increased to the point where the alkene began to react and form the unwanted side product. These experiments conclusively prove the need for TEAB as a redox catalyst to generate an electrophilic source of selenium. The finding of Torii that the direct oxidation of diphenyl diselenide to a mixed peroxide is readily achieved in appropriate conditions is not supported by this investigation (section 2.1).

The selenoxide elimination is a well-known reaction, occurring spontaneously at room temperature as soon as the selenoxide has formed. As previously mentioned, the selenoxide elimination requires a source of oxygen for the conversion of **28** into the selenoxide **29**. Having already endeavoured to exclude oxygen from the reaction by drying and degassing the solvent, oxygen was now permitted in the reaction. The solvent was treated with water (1% v/v) and the reaction vessel left open to the atmosphere. The intermediate **28**, synthesised non-electrochemically, was electrolysed in methanol in a range of conditions.

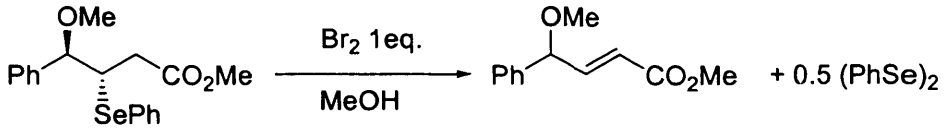
The anticipated increase in the rate of the elimination when the reaction was carried out in the presence of oxygen was not observed. The conversion of **27** to **30** proceeded in low yield unless TEAB was added to the reaction. The effect of other electrolytes on the elimination when used in place of TEAB was negligible. This is strong evidence that bromide or bromonium plays a crucial part in the elimination step.

Table 2-11 Electrochemical formation of **30** from **28**

Entry	F/mol	Oxygen	Electrolyte	Acid	Time	Yield
1	2.9	Permitted	TEAB	H_2SO_4	4 hrs	**69%**
2	2.9	Permitted	None	H_2SO_4	4 hrs	12%
3	2.9	Excluded	TEAB	H_2SO_4	4 hrs	**65%**
4	2.9	Excluded	None	H_2SO_4	4 hrs	14%
5	2.9	Permitted	TEAB	None	4 hrs	**61%**
6	4.5	Excluded	None	None	6 hrs	16%
7	2.9	Permitted	Et_4NBF_4	H_2SO_4	4 hrs	8%
8	6.0	Excluded	Et_4NBF_4	None	8 hrs	14%
9	2.9	Permitted	Et_4NPF_6	H_2SO_4	4 hrs	12%
10	6.0	Excluded	Et_4NPF_6	None	8 hrs	17%

Conditions: selenide **28** (0.1 mmol) in methanol (7 ml), yields from GC-MS (naphthalene as internal standard) except those in bold type.

Consideration now had to be given to a mechanism that accounted for the elimination relying on bromide not oxygen. To this end the intermediate **28** was treated with a solution of bromine in methanol. The result of this reaction was the immediate elimination of the selenium moiety to give, after workup, the alkene **30** and diphenyl diselenide both in quantitative yield.



28 **30**

Figure 2-27 Bromine induced elimination to the alkene

Combining this observation with the rest of the experimental information about the mechanism gives the catalytic cycle shown in Figure 2.28.

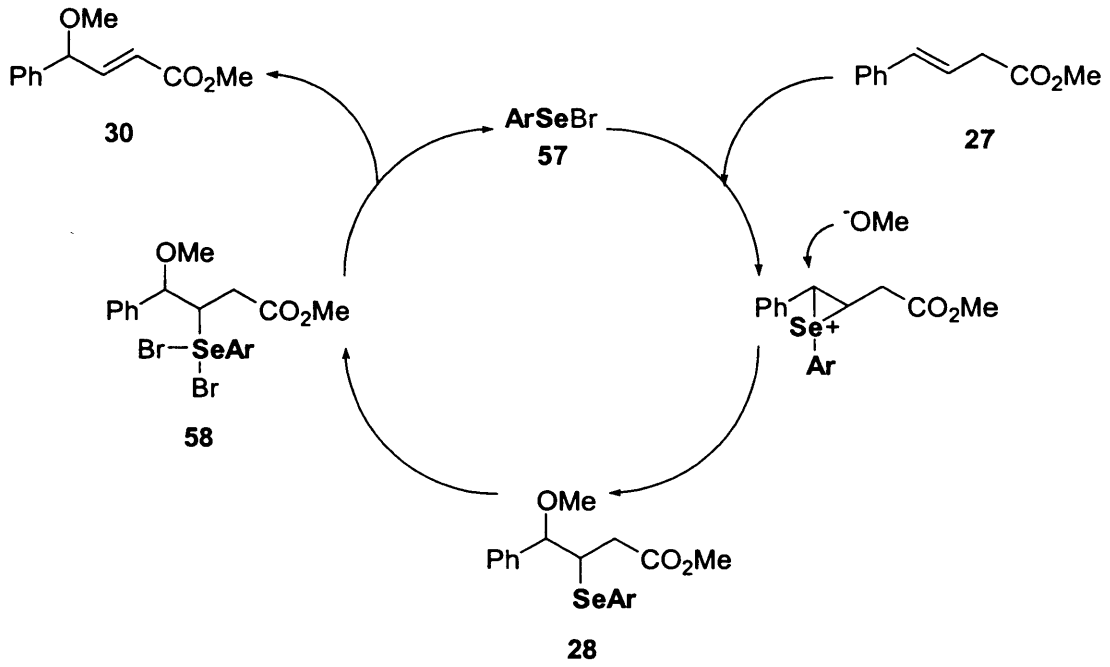


Figure 2-28 Proposed mechanism for the catalytic use of chiral diselenides for the conversion of alkenes into allylic ethers

From this cycle it is clear that bromide fulfils two different roles as it mediates two separate reactions. The role of sulphuric acid is tentatively assigned to that of electrolyte, having no direct influence on the mechanism but affecting the overall yield of the reaction. Attempts to identify the selenurane **58** by GC-MS were not successful due to the unstable and short-lived nature of this species. It was also not possible to detect the presence of any chiral selenenyl bromide species using GC-MS, again due to the unstable nature of these compounds. The chiral diselenides themselves are unstable in GC-MS conditions. This catalytic cycle is believed to stop working due to the gradual decomposition of the chiral selenium moiety. To increase the turnover of the catalyst it is clear that this decomposition needs to be controlled. Under these mild electrochemical conditions the alkene is stable and the electrochemical recycling of the redox mediator can be sustained almost indefinitely.

Chapter 3

New Approaches to the Design of Chiral Diselenides

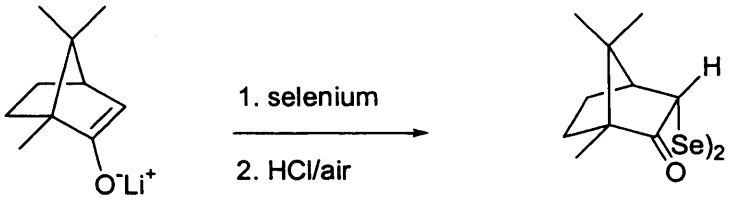
The success of the commonly employed design of the efficient chiral selenium electrophile has been attributed to two factors;

1. the locking of the molecules conformation by coordination of the positively charged selenium by the lone pair of the heteroatom.
2. the drawing of the chiral centre closer to the reaction centre as a consequence of this coordination.

Figure 3-1 Selenium heteroatom interactions

The existence of these interactions has been proven by NMR spectroscopic measurements and by X-ray structure determination in addition to theoretical calculations.[58] An alternative approach that seeks to take advantage of both of these factors is the exchanging of position of the selenium and the heteroatom. Coordination with heteroatom is still possible, but now the reactive centre is on the chiral centre.

The synthesis of such compounds presents a number of challenges, such as the need to use an enantiomerically pure precursor and the introduction of reactive selenium at the chiral centre. An example where this has been achieved is diselenide **14**. Elemental selenium reacts with the lithium enolate of camphor followed by air oxidation to produce **14**, which can be easily converted into the electrophilic triflate.[33]

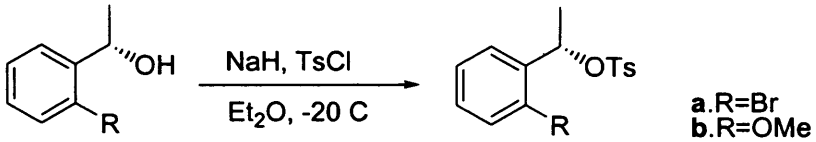


14

Figure 3-2 Synthesis of the camphor based diselenide

3.1 Chiral Diselenides by Exchange of Selenium and the Heteroatom

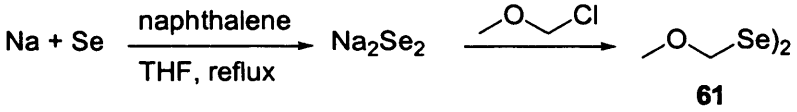
As an alternative to the chiral enolate method alcohols **59a** and **59b** were synthesised from the corresponding ketones by reduction with DIP-Cl, as a single enantiomer and converted into the corresponding tosylates **60a** and **60b**, with the intention of carrying out an S_N2 reaction with a suitable selenium nucleophile.



59a/b **60a/b**

Figure 3-3 Synthesis of the chiral tosylate

As this approach is not compatible with electrophilic elemental selenium, an alternative selenium source was required. From investigations into solid supported chiral selenium electrophiles came the discovery of the methoxymethyl protected diselenide.[59] MOM diselenide **61** was synthesised in 45% overall yield from elemental selenium via disodium diselenide according to the published procedure.[60]



61

Figure 3-4 Synthesis of dimethoxymethyl diselenide

The methoxymethylseleno group has been successfully substituted onto benzene rings by reaction with a lithiated aromatic compound, then reacted in the same manner as the corresponding diselenide to generate the electrophilic species.

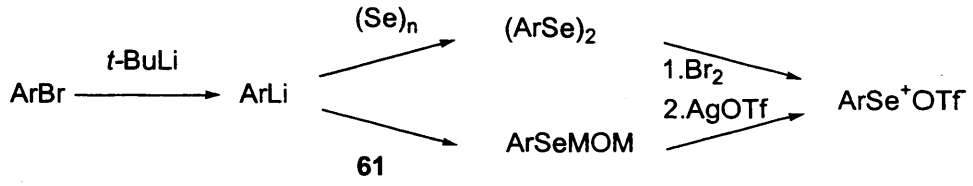


Figure 3-5 Two routes to the synthesis of selenenyl triflates

As previously discussed, there are a number of methods available for the generation of selenium nucleophiles, the simplest being the reduction of a diselenide with sodium borohydride. Treatment of MOM diselenide with sodium borohydride produced the selenolate **62** (probable structure [(MOMSeB(OEt)$_3$)Na] by analogy to the behaviour of (PhSe)$_2$).[61]

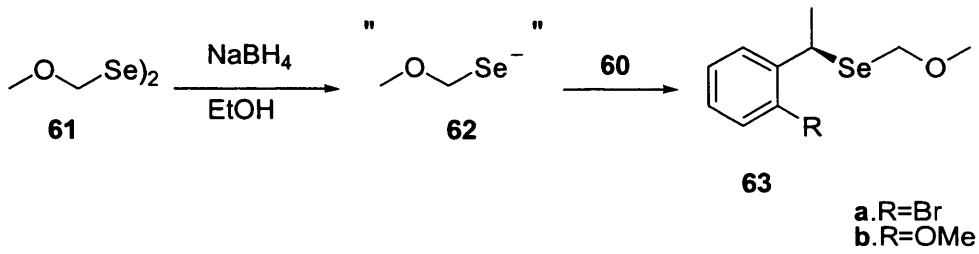


Figure 3-6 Synthesis of novel chiral selenides

In addition, the "naked" sodium salt of MOM selenide was formed by sonication of MOM diselenide with sodium in the presence of naphthalene though this proved more difficult to handle due to its greater reactivity than the complexed selenolate. The selenolate was treated with tosylate **60a** to give the selenide **63a** in 15% yield. Though lacking suitable heteroatom for coordination, this selenide was converted into the selenenyl triflate and reacted with styrene in the presence of methanol to give **64a** in 29% yield (0% *de*).

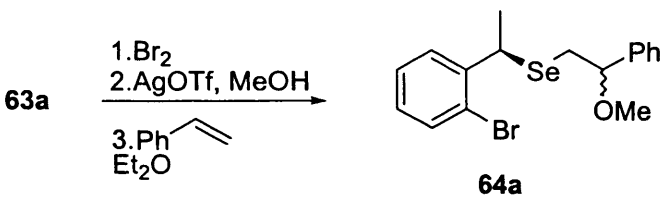
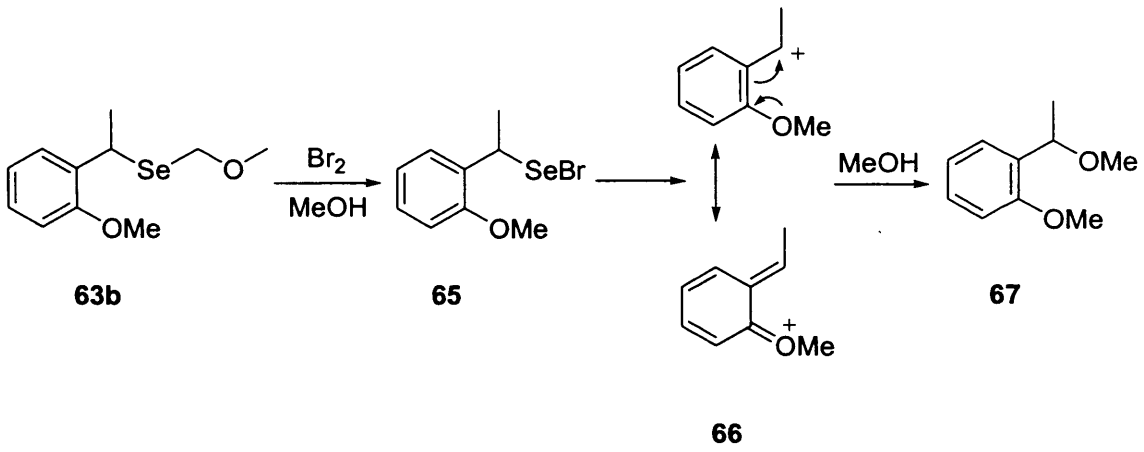


Figure 3-7 Selenomethoxylation of styrene with novel selenide **63a**

The low selectivity was attributed to the absence of a coordinating heteroatom. Consequently, the selenide **63b** was synthesised from **60b**. The presence of the methoxy group however had a profound effect on the reactivity of the selenide. After treatment with bromine and silver triflate, no reaction with styrene was observed. Further analysis revealed that the selenide had decomposed before the alkene was introduced. Various conditions were tried but each time decomposition occurred. The decomposition was rationalised by considering the resonance structures made possible by the lone pairs on the oxygen. Stabilisation of the intermediate **66** drives the elimination of the selenenyl bromide group. The cation is trapped by methanol to produce the diether **67** in 58% yield, recovered from the reaction mixture along with elemental selenium.



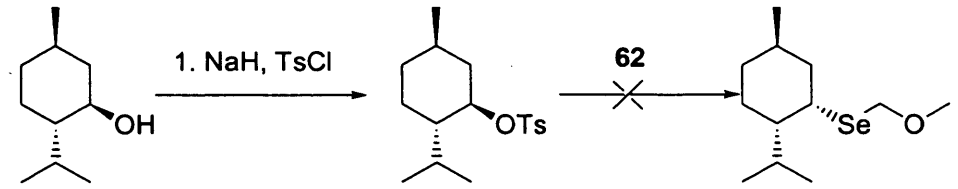
63b **65** **66** **67**

Figure 3-8 Elimination of selenium to produce diether

3.2 Chiral Selenium Electrophiles derived from Chiral Pool Compounds

A different approach was clearly required to take into account this unexpected behaviour. The direct exchange of position of the selenium with the heteroatom had been proven as unworkable in an aryl based structure. An alternative design would need to incorporate an alkyl based structure with less possibility of resonance stabilisation. The first target to take this modification into account was **69**. The tosylate derived from menthol is known to readily undergo S_N2 reactions with suitable nucleophiles.[62] Starting from readily available menthol, the selenide **69** was to be synthesised in two steps using the same methodology as the previous example. The tosylate was synthesised according to the literature procedure. Reaction of menthyl tosylate with selenolate **62** did not result in substitution despite several attempts in

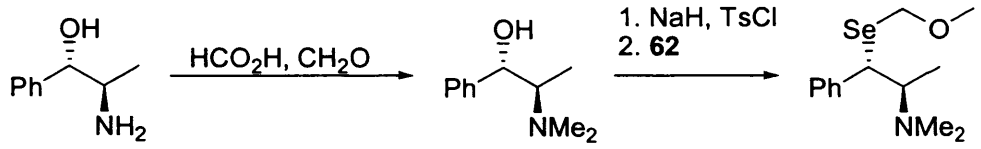
different conditions. The mesylate was also synthesised but this failed to react in the desired manner, undergoing hydrolysis to produce menthol.



68 **69**

Figure 3-9 Selenide from menthol

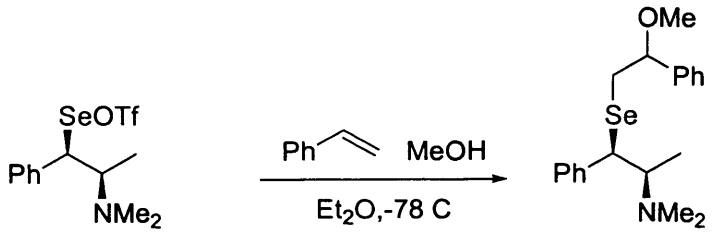
Concerned that the bulky isopropyl group was hindering the S_N2 displacement of the tosyl leaving group, a less hindered substrate was required. To this end, selenide **71** was synthesised from norephedrine in 3 steps, albeit in only 18% yield. Again, the selenium was introduced as the MOM selenolate allowing rapid access to the electrophilic species. The key advantages of this target are the availability of the starting material at low cost enantiomerically pure, the presence of a heteroatom in an alkyl position and conceivably the potential benefit of an additional chiral centre.



70 **71**

Figure 3-10 Synthesis of the norephedrine derived selenide

The selenenyl triflate **72** was reacted with styrene in the presence of methanol to produce what is thought to be selenide **73** in 17% yield but with 0% *de* (assignment based on ^{1}H NMR spectra only).

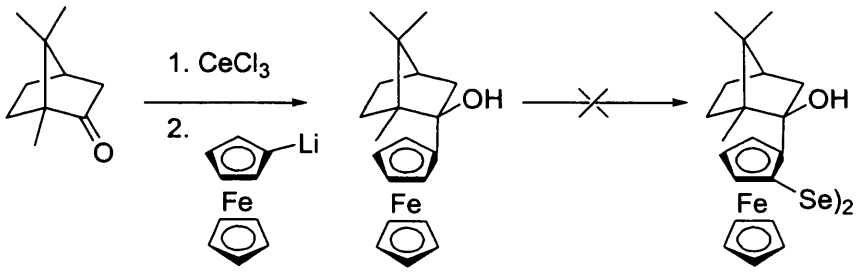


72 **73**

Figure 3-11 Reaction of the norephedrine selenide

3.3 Chiral Selenium Electrophiles Derived from Organometallic Sandwich Compounds

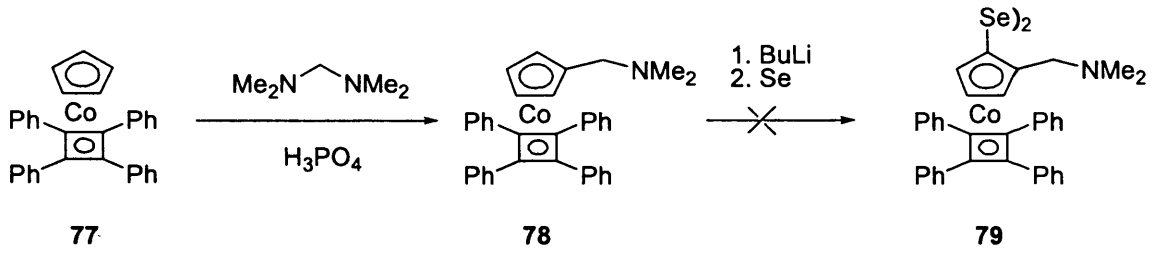
This total lack of diastereoselectivity questioned the premise on which this investigation had been carried out, that more efficient chiral selenium electrophiles could be made by placing the electrophilic selenium on a chiral centre. An alternative approach was to consider the incorporation of a different form of chirality into the selenium electrophile. For example, a planar chiral diselenide has been synthesised by Uemura. This diselenide possesses the same heteroatom selenium 1-3 relationship as previously discussed, but exhibits planar chirality as a result of its ferrocene backbone. Despite the efficiency of the corresponding electrophilic species, this diselenide is rarely employed, due to the difficult nature of the synthesis. An alternative ferrocene based diselenide more easily synthesised could therefore be of value. It was decided to make use of a chiral pool molecule to provide a chiral centre. Camphor was chosen and was reacted with ferrocene according to a literature procedure to give ferrocenyl camphor **74**.[63] This compound was subjected to a variety of different reaction conditions in an attempt to introduce selenium to the aromatic ring. All attempts to reach this target failed.



74 **75**

Figure 3-12-Synthesis of the ferrocene diselenide

A more ambitious target was devised incorporating selenium onto a cobalt sandwich complex to obtain a planar chiral diselenide. The known cobalt complex **77** was synthesised in one step from a source of cobalt(tristriphenylphosphine)chloride **76**, diphenyl acetylene and sodium cyclopentadienyl.[64] This was then treated with *N,N*,dimethyl bisaminomethane to form the aminomethylated complex **78** in 3% yield. Attempts to introduce selenium to the Cp ring using a range of conditions for the lithiation were not successful and diselenide **79** was not obtained.



77 78 79

Figure 3-13 Synthesis of the cobalt sandwich complex diselenide

The lack of ability of reagent **72** to transfer chiral information marked a turning point in this investigation. Although the camphor derived diselenide **14** has proven itself an efficient reagent, the principle of merely having the selenium on a chiral centre has been proven to be ineffective as a design principle for efficient chiral selenium electrophiles. What makes **14** a better reagent than **71** is as yet unclear, and a greater understanding of the process for the transfer of chiral information from a selenium electrophile to a substrate may be required before a definitive answer to this question can be found.

Chapter 4

Variation of the Heteroatom of Chiral Diselenides

As previously discussed, all efficient chiral selenium electrophiles possess a heteroatom, normally in a 1-3 relationship to the selenium atom. Oxygen has been the heteroatom of choice in the majority of these compounds, though several nitrogen compounds are known. Most recently, sulphur has been employed, and initial investigations support the view that the sulphur-selenium interaction is more significant than either oxygen-selenium or nitrogen-selenium interactions. Some of the highest selectivities observed to date in a range of selenofunctionalisations of alkenes have been achieved using these sulphur reagents.[54] More importantly, the sulphur analogues of certain oxygen diselenides are more efficient reagents for certain substrates.

This recent finding has thrown the spotlight onto the role of the heteroatom, causing speculation as to which heteroatom would have the most positive effect on the efficiency of the corresponding diselenide.

X	R	R^1	Yield	*de*
S [54]	H	H	80%	92%
O [66]	H	H	67%	83%
S [54]	OMe	H	72%	96%
O [55]	OMe	H	55%	96%
S [54]	OMe	Me	75%	96%
O [55]	OMe	Me	50%	85%

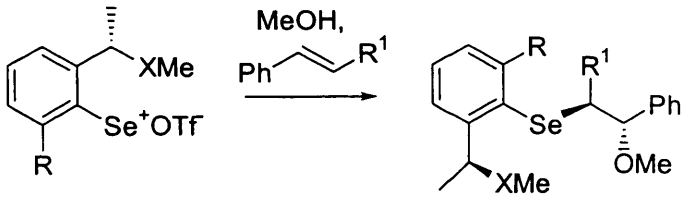
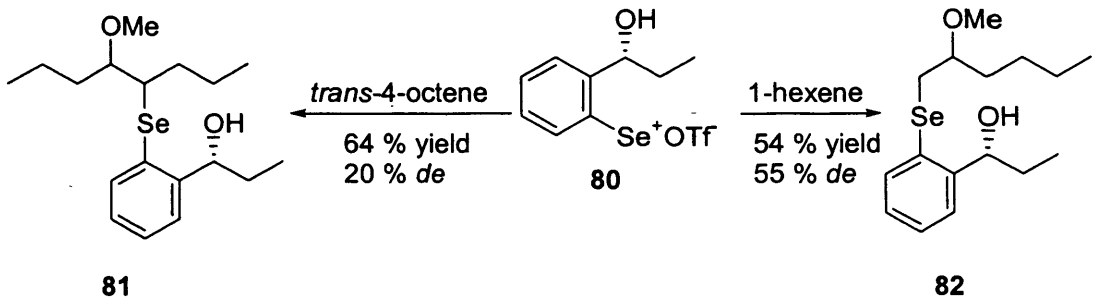


Table 4-1 Comparison of S and O selenium electrophiles for the methoxylation of alkenes

The efficiency of the oxygen containing diselenides is also disappointing in reactions involving linear aliphatic alkenes. Reaction of triflate **80** derived from diselenide **37** with 1-hexene and with *trans*-4-octene proceeds with low diastereoselectivity.



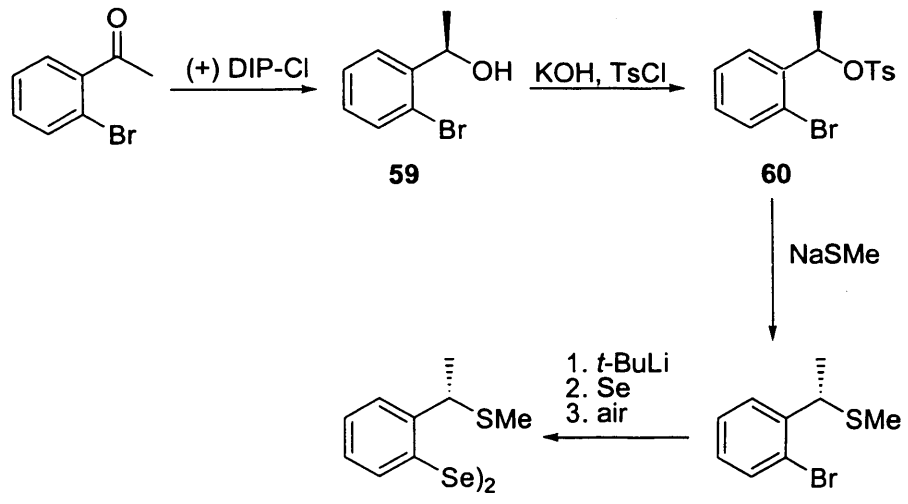
81 **82**

Figure 4-1 Additions to alphatic alkenes

4.1 Synthesis a Phosphorus Substituted Diselenide

To further the work already done in this area diselenides with alternative heteroatoms would now be synthesised. The first objective was to synthesise a phosphine diselenide and to study the reaction of the corresponding electrophile. A synthetic strategy was required that would enable convenient modification of the side chain.

Tiecco showed that the side chain of 2-bromoacetophenone could be conveniently modified in two steps, enabling the exchange of a hydroxyl group for a thioether.[54]

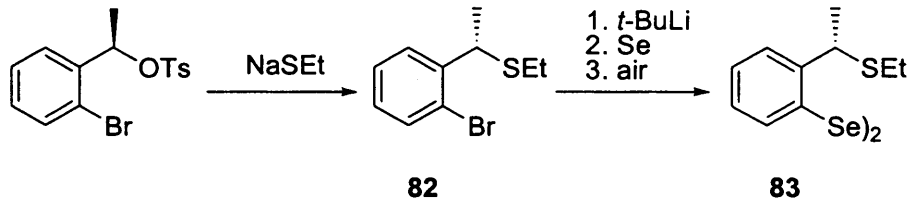


59 **60**

Figure 4-2 Synthesis of sulphur containing diselenide

Treatment of **59** with a suitable base in the presence of tosyl chloride produces tosylate **60**, which undergoes an S_N2 reaction with sodium methane thiolate to give a thioether.

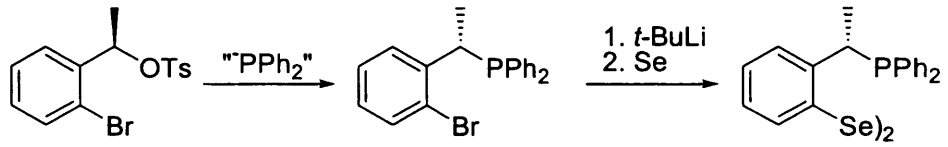
This can be converted into the corresponding diselenide in one further step. Following this methodology and employing sodium ethane thiolate in place of sodium methane thiolate, the precursor **82** and diselenide **83** were synthesised. The diselenide was used in the electrochemical investigation as mentioned previously.



82 **83**

Figure 4-3 Synthesis of the sulphur substituted diselenide

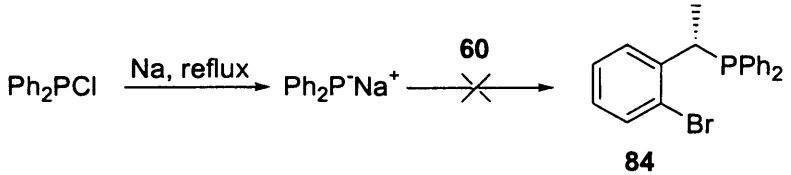
Extending this methodology to the synthesis of the phosphorous analogue **85** would clearly require a source of nucleophilic phosphorous.



59 **84** **85**

Figure 4-4 Plan for the synthesis of the phosphorous diselenide

This simplest reagent for this conversion is synthesised by refluxing diphenylphosphine chloride with sodium to form sodium diphenyl phosphine.[67] This can react with a tosylate to form the desired phosphine, with complete inversion of stereochemistry. Accordingly, sodium diphenyl phosphine was synthesised and added to the tosylate **60**. However, after several hours stirring followed by workup, no trace of the desired product was detected, though clearly a range of reactions had taken place. Repeating this reaction in different conditions produced the same result each time.



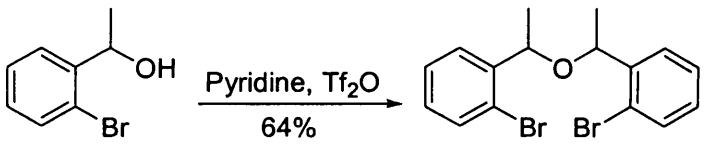
84

Figure 4-5 Conversion of tosylate into phosphine

Though the tosylate had not been completely consumed during the course of the reaction, there were a large number of side reactions occurring. Attempts to separate this complex mixture failed to result in the isolation or characterisation of any of these side products.

Another example of the exchange of an alcohol for a phosphine group makes use of a borane protecting group on the phosphorous, preventing unwanted oxidation to the phosphorous (V) compound.[68] The presence of this protecting group simplified the purification of that particular phosphine and resulted in a more stable product, though adding a further step to the synthesis for the deprotection. For the deprotection, the authors descried the use of tetrafluorohydroboric acid dimethylether complex, producing the phosphine which required no purification after anaerobic workup.

A different precursor to the tosylate was also required due to the low solubility of the tosylate **60** in organic solvents. This insolubility resulted in long reaction times, in some cases too long, as unstable nucleophiles decomposed in the reaction. The attraction of using tosylates was the ease with which stereochemical integrity could be preserved. For this investigation, the need to prove that these reagents could be synthesized initially overrode the need to synthesise these reagents enantiomerically pure. An alternative leaving group was therefore needed, one easily synthesised from the alcohol. Whilst the triflate seemed the obvious choice, the fact that the substitution was to occur in the benzylic position was cause for concern, as benzyl triflates are highly reactive.[69] Attempts at converting the alcohol **59** into the corresponding triflate had led to the exclusive formation of the dimer **86**, despite the low temperature used for the reaction.



86

Figure 4-6 Reaction of the triflate to form the dimer

The halides **87** and **88** were therefore synthesised according to literature procedures.

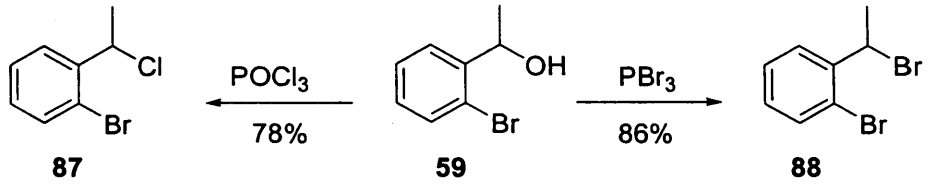


Figure 4-7 Halide precursors from the alcohol

Starting from the racemic alcohol, the reactions were conducted at room temperature, as there were no stereochemical considerations. However, chloride **87** proved to be almost as insoluble as the tosylate **60**. The bromide **88** was highly soluble and was used for the next step.

Commercially available diphenyl phosphine borane complex was treated with *n*-BuLi to form the lithiated, nucleophilic species **89**, which was added to bromide **88**. The desired product **90** formed in 67% yield.

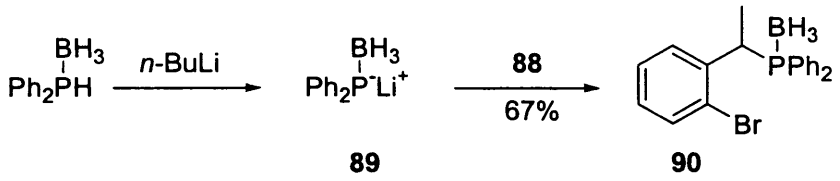


Figure 4-8 Synthesis of the borane protected phosphine

It was decided to attempt the lithiation of **90** before removal of the borane protecting group to simplify the handling of the product. Repeated attempts in a range of conditions to lithiate **90** failed, with unreacted starting material or the dehalogenated analogue being recovered each time.

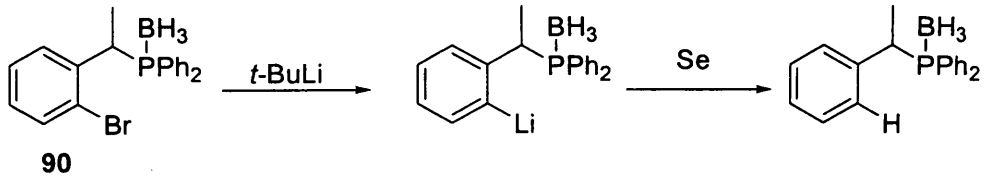
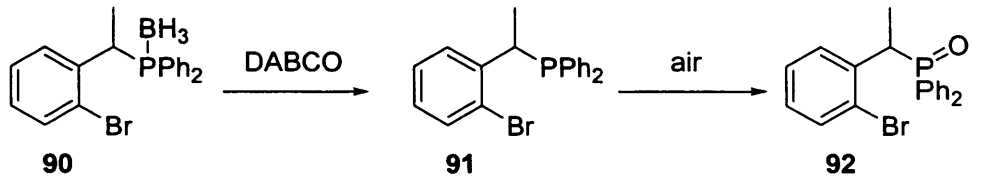


Figure 4-9 Dehalogenation of the borane protected phosphine

It now seemed inevitable that **90** had to be deprotected and so it was treated with 10 equivalents of DABCO. The reaction was followed by ^{1}H NMR and the borane moiety was observed to be quickly removed giving **91**. Following a literature procedure for

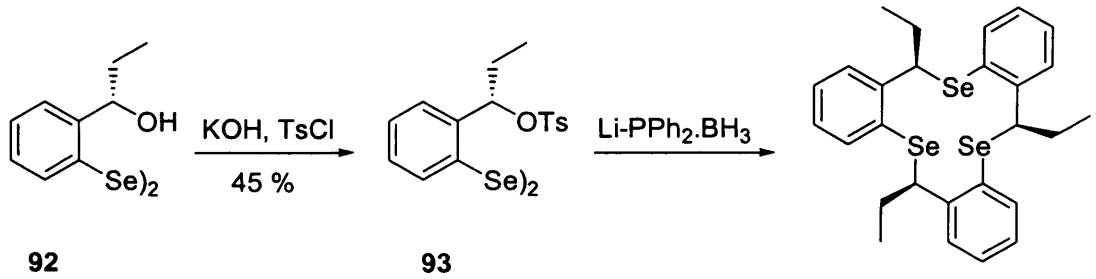
this deprotection, the solution was filtered through basic alumina to remove the DABCO before the solvent was removed. This very brief exposure to air resulted in the partial oxidation of **91** to **92**. The separation of this mixture proved too difficult and so air was pumped through the solution to complete the oxidation. The resulting mixture contained a number of impurities but with all of **91** converted into **92**. Attempts to lithiate this compound also failed.



90 **91** **92**

Figure 4-10 Deprotection and subsequent oxidation of the phosphine

An alternative approach to the synthesis of the phosphorous diselenide involves manipulation of the side chain after the introduction of the selenium atom onto the aromatic ring. Accordingly the diselenide **92** was treated with potassium hydroxide and tosyl chloride to give the tosylate **93**. This tosylate was then treated with the nucleophilic phosphorous source that had been used previously to substitute the alcohol moiety with a phosphine. The reaction resulted in a large number of side products. Whilst the ethyl analogue of the desired phosphine **85** was not obtained, one of the side products isolated (27% yield) was tentatively assigned the structure **94**, based on compelling evidence from high resolution mass spectrometry and proton, carbon and selenium NMR experiments.



92 **93** **94**

Figure 4-11 Side chain manipulation after the introduction of selenium on the aromatic ring

4.2 Selenium Diselenides

Having encountered serious difficulties with the phosphorous target, alternative heteroatoms were considered, including selenium itself. If a similar synthetic strategy to the previous target were to be used then a source of nucleophilic selenium would be required. There has been a large amount of research conducted into nucleophilic selenium and a range of options exists for the synthesis of alkyl and aryl selenium nucleophiles. The easiest synthesis involves treatment of a diselenide with sodium borohydride in ethanol. The complex **95** forms quickly and is easier to handle than the 'naked' sodium salt, whilst being sufficiently reactive for many applications.

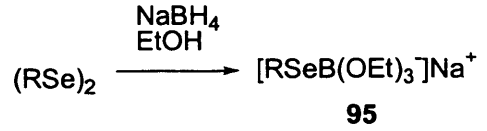


Figure 4-12 Formation of the nucleophilic selenium source

As with the phosphorous target, the synthetic pathway started with the conversion of 2-bromoacetophenone into the enantiomerically pure tosylate **60**. Treatment of **60** with **95** (R=Ph) resulted in selenide **96a**, though in disappointing yield. Again, the problem with the yield seemed to be a consequence of the low solubility of the tosylate. Synthesis of the racemate via the bromide proceeded in a much higher yield. The synthesis of **96b** (R=Me) was also achieved in similar yield. Treatment of **96b** with *t*-BuLi followed by the addition of selenium powder resulted in the formation of the desired diselenide **98b** in 35% yield. In addition to this diselenide, the cyclic diselenide **99** was isolated from the reaction in 56% yield.

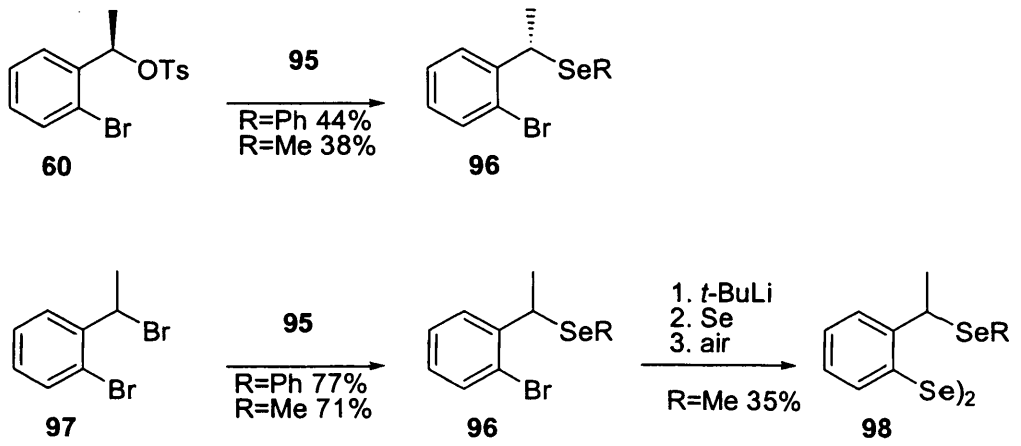
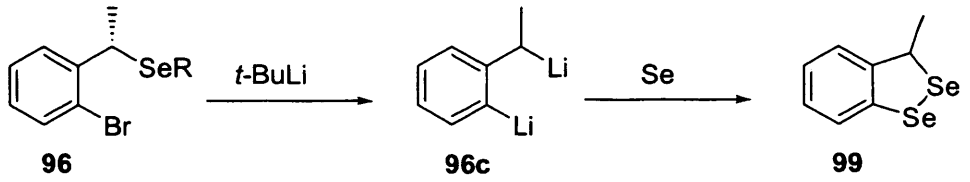


Figure 4-13 Conversion of the tosylate into selenides

The mechanism for the formation of **99** is not completely clear. It is known that benzylic phenyl sulphides can be converted to the corresponding organolithiums by uncatalysed reductive metalation using lithium metal.[70] If this metalation can be achieved with benzylic selenides, then **96** can be lithiated in two positions to give the intermediate **96c**. Treatment with selenium metal followed by oxidative workup would produce **99**. There is however, no proof yet that this occurs in selenides.

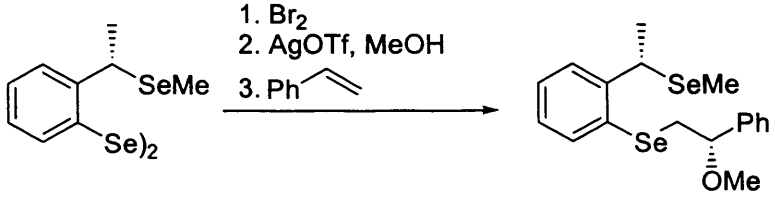


96 **96c** **99**

R=Ph 43 %
R=Me 57%

Figure 4-14 Formation of the cyclic diselenide

Reaction of the electrophile derived from diselenide **98** with styrene produce the selenide **100** in good yield (73%) with high selectivity (81% *de*). However, despite the large number of attempts made at the synthesis of diselenide **98**, it has yet to be successfully repeated. Most of these experiments resulted in the formation of the cyclic diselenide **99**. This problem remains unresolved.

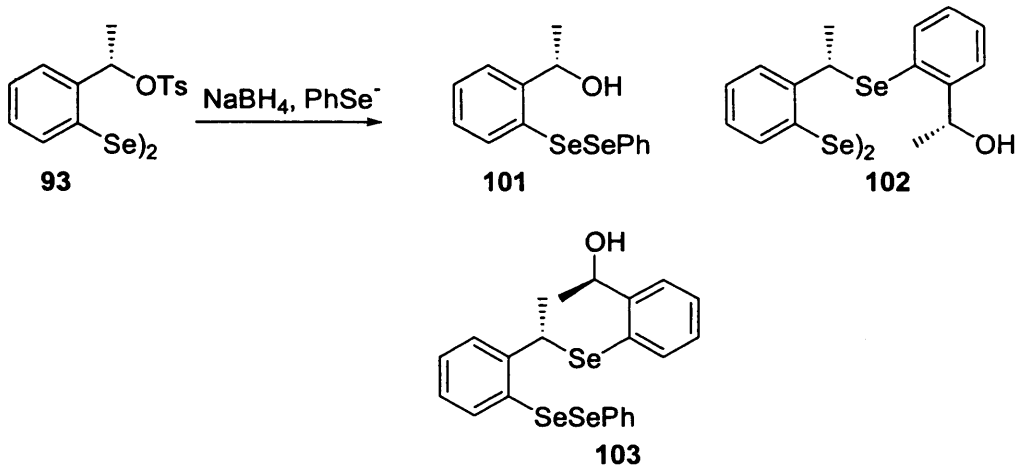


98 **100**

Figure 4-15 Reaction of selenium diselenide with styrene

This reaction indicated the intolerance of the side chain to organolithium reagents, so an alternative approach would be required avoiding the use of these reagents. The first option was to introduce the aryl selenium before the manipulation of the side chain. One drawback of this approach was the method used for the introduction of the selenium of the side chain. If the nucleophilic selenium was generated by using sodium borohydride, then any traces of sodium borohydride remaining in the mixture would

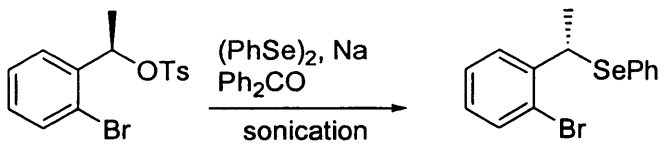
reduce the diselenide **98** to the corresponding selenolate. This could produce a mixture of **101**and **102** as well as **103**.



93 101 102 103

Figure 4-16 Potential side products

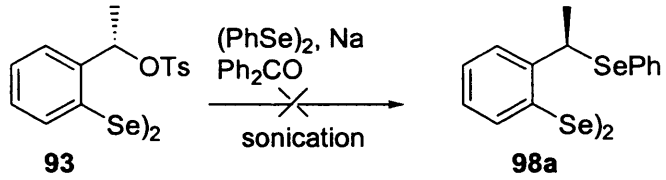
A source of nucleophilic selenium was therefore required which did not need a reducing agent for its formation. The naked selenolate fulfils this requirement. There are several methods described for the synthesis of sodium phenylselenolate including treatment of diphenyl diselenide with sodium hydride and refluxing sodium with diphenyl diselenide.[71] An alternative route makes use of sonication to effect the rapid formation of sodium phenylselenolate.[72] This reaction requires an electron carrier such as benzophenone or naphthalene to enable the complete conversion of diphenyl diselenide in under 3 hrs. The selenolate forms as a white suspension that can easily be added to a reaction. Sodium is not a strong enough reducing agent to reduce the diselenide directly and so any unreacted sodium will not affect the reaction. This method has previously been used nucleophilic substitution of achiral tosylates with a phenyl selenyl group.



59 96

Figure 4-17 Conversion of tosylate into selenide with sodium phenyl selenolate

The reaction of tosylate **59** with sonically generated phenyl selenolate lead to the selenide **96a** in 45% yield, more importantly with complete inversion of stereochemistry, as determined by HPLC. Having established this as a viable method for the substitution of the tosylate, the diselenide was synthesised, treated with potassium hydroxide and tosyl chloride to produced tosylate **93**. Reaction of this tosylate with sodium phenylselenolate failed to give the desired molecule. After six hours, diphenyl diselenide was isolated along with the starting diselenide though less enantiomerically pure, as determined by the presence of diastereoisomers in the ^1H NMR spectrum.

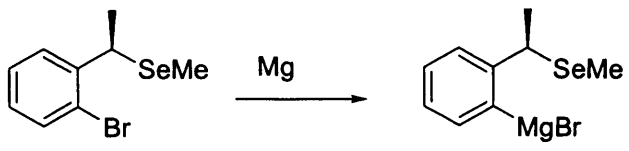


93 **98a**

Figure 4-18 Reaction of the diselenide tosylate with sodium phenylselenolate

An alternative solution to the problem of side chain intolerance of organolithium reagents involves different methods for the addition of selenium to the aromatic ring. The normal established method is the lithium halogen exchange of the bromo precursor with butyllithium followed by the lithium selenium exchange. Other methods for halogen selenium exchange exist, including the reaction of the bromo precursor with disodium diselenide. Treatment of **96** with disodium diselenide however failed to give any reaction, even after refluxing for 48 hours in THF.

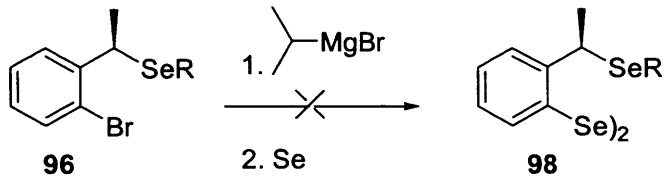
Finally, diselenides have been synthesised by reaction of elemental selenium with Grignard reagents.[73] The formation of Grignard reagent **104** was attempted by reaction of **96b** with magnesium.



96b **104**

Figure 4-19 Grignard precursor to the diselenide

A range of techniques were used to try an initiate this reaction, including disturbing the surface of the magnesium by mechanical action, washing the magnesium with dilute acid and using iodine or 1,2 dibromoethane failed to generate **104**, with just the bromo precursor **96** being recovered. Generation of **104** was also attempted by treating **96** with the isopropyl magnesium bromide and also ethyl magnesium bromide. There are many literature examples where magnesium has been successfully exchanged with halogens using these reagents enabling conversion of sensitive substrates into Grignard reagents.[74] Isopropyl magnesium bromide was synthesised from 2-bromopropane and magnesium then added to selenide **96b**. Selenium was then added, but no reaction was observed, with starting material and diisopropyl diselenide being recovered. This reaction was repeated in a variety of different conditions without success.



96 **98**

Figure 4-20 Diselenide *via* a Grignard reagent

The use of a protecting group on the aryl selenium offered an alternative to the diselenide. As previously discussed, the methoxymethyl (MOM) selenium group can be used as a precursor to the corresponding electrophile. The MOM group is stable to reducing agents and would therefore tolerate the presence of sodium borohydride in a reaction. Selenide **105** was synthesised and the tosylate formed in the established manner. This tosylate **106** formed in low yield but was more soluble than tosylate **59**. Treatment of this tosylate with phenylselenolate **95** did not produce the target selenide **107**, giving the starting alcohol **59** after aqueous work-up.

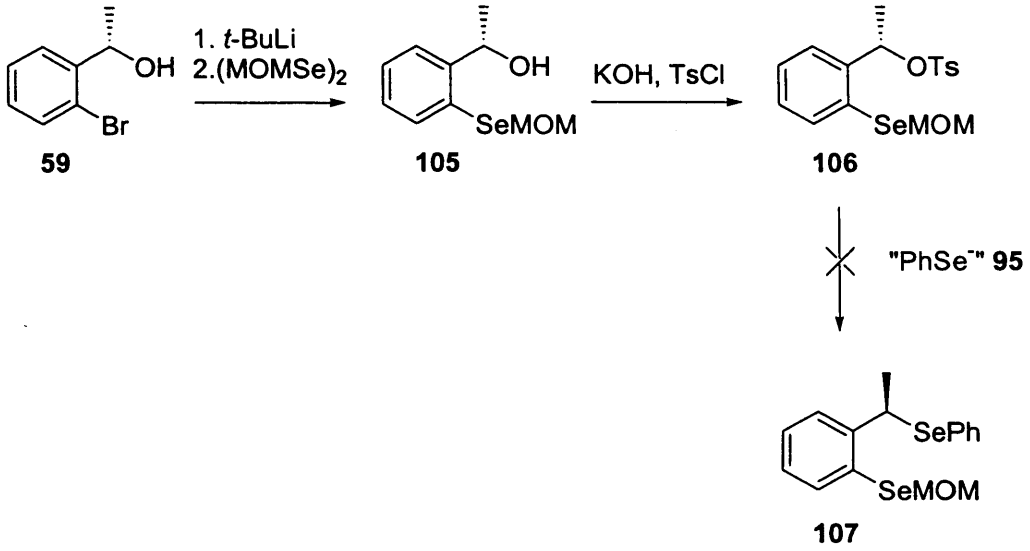


Figure 4-21- Reaction of MOM selenide with nucleophilic selenium

4.3 *Ortho* Substituent Effect

It has been shown that introducing a coordinating substituent in the *ortho* position of a chiral diselenide can induce a greater conformational rigidity to the corresponding electrophile leading to a more efficient transfer of chiral information.

R	R^1	Alkene	Yield	*de*
H	SMe[49]	Styrene	80%	92%
OMe	SMe[49]	Styrene	72%	96%
H	OH	Styrene	67%	86%
OMe	OH[59]	Styrene	55%	96%
H	SMe[49]	Cyclohexene	77%	64%
OMe	SMe[49]	Cyclohexene	75%	82%

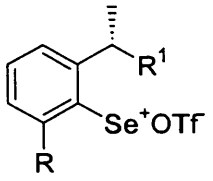
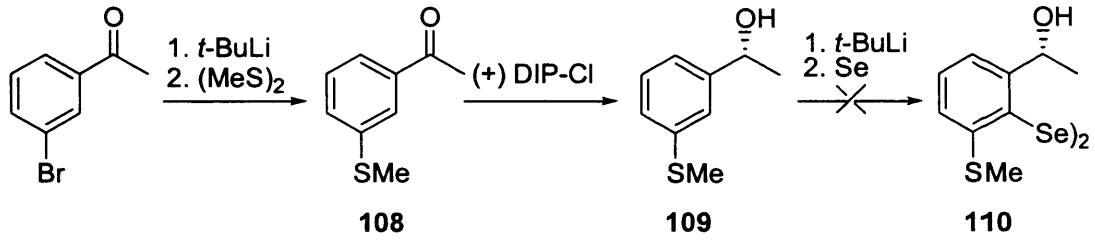


Table 4-22 Efficiency of selenium electrophiles in the selenomethoxylation of alkenes

The recent discovery of the importance of the sulphur-selenium interaction prompted us to consider the effect of using sulphur in place of oxygen in the *ortho* position. Starting from commercially available 3-bromo acetophenone, the thioether **108** was synthesised in one step following a literature method and reduced with DIP-Cl to the enantiomerically pure alcohol **109**. Treatment of **109** with *t*-BuLi failed to produce the

desired diselenide **110**, although there was no trace of starting material in the reaction mixture. ^{1}H NMR and GC-MS analysis of the reaction mixture revealed a large number of side products. A perusal of the literature of thioanisoles reveals the acidic nature of the thiomethyl protons, indicating the strong probability that deprotonation occurred at this point rather than on the aromatic ring.[75] This lithiated species would be highly reactive and account for the large number of side products.



108 **109** **110**

Figure 4-23 Synthesis of the *ortho*-thioanisole diselenide

A milder base would be required, though a base strong enough to deprotonate the aromatic ring. Various conditions were employed including the use of *n*-BuLi and TMEDA, each time without sucsess. There was no possibility of manipulating the *ortho* substituent after selenium was added because of the reactivity of selenium toward the reagents required for this manipulation. This target remains unmade.

In this search for more efficient reagents, the most interesting results have come from the synthesis of diselenides **83** and **98**. The use of **83** in the electrochemical reaction produced the highest selectivity observed, vindicating this search for superior reagents.

Chapter 5

Outlook

The electrochemical approach to the use of chiral diselenides in the functionalisation of carbon carbon double bonds has been investigated in some depth. The main aim of the electrochemical use, to enable the use of chiral diselenides in catalytic amounts, is of high importance, given the toxicity of selenium compounds. To satisfy this need, an extension of this investigation would have to focus primarily on increasing the yield of the reactions. This may involve employing diselenides more stable in electrochemical conditions, or possibly further optimisation of the conditions themselves. Either way, the reasonably high selectivity achieved by the use of a sulphur diselenide offers hope that the reaction can work at increased temperatures. Development of chiral selenium electrophiles based on the principles discussed previously may yet prove valuable, but this investigation has not provided any evidence to support this. The use of chiral pool molecules as the source of chirality remains an attractive prospect, though clearly a different approach to this investigation would seem most conducive.

Conclusion

It has been shown that chiral non-racemic diselenides can be used in a one-pot electrochemical selenenylation-deselenenylation sequence to convert alkenes into allylic ethers. Furthermore, it has been shown that these diselenides can be recycled *in situ* and thus used in catalytic amounts for this conversion. Using 10 mol% of a chiral diselenide, yields of up to 60% could be achieved, along with stereoselectivities of up to 68%. The scope for this methodology has been systematically investigated using different substrates and different diselenides, revealing some of the limitations of this approach.

A new approach to the design of chiral diselenides has been investigated resulting in the synthesis of three novel chiral selenium electrophiles and a new method for the introduction of selenium bearing a protecting group onto a chiral centre. The efficiency of these reagents has been studied and partially determined. The use of natural products

as the source of chirality in chiral selenium reagents has been investigated. The synthesis of novel organometallic diselenides has been advanced to within one step of the target. During the search for more efficient reagents for the electrochemical reaction, several novel compounds have been synthesised, some of them serendipitously. The first selenium substituted chiral diselenide has been synthesised and investigations into its efficiency begun. The synthesis of the first phosphorus substituted diselenide has been advanced to within one step of the target.

Chapter 6

Experimental

All experiments were carried out using standard laboratory equipment. Reactions requiring the exclusion of oxygen were carried out under an argon atmosphere. Diethyl ether and THF were distilled from sodium benzophenone ketyl, dichloromethane from calcium hydride and methanol from magnesium with iodine. Cooling baths were prepared from dry ice and acteone, or in the case of longer experiments, a *Haake EK 90* immersion cryostat was employed.

The electrochemical reactions were carried out under argon where required in a custom-made reaction vessel or in a sample vial (20 mm x 80 mm) using platinum foils (14 mm x 22 mm) at a constant current provided by a *Heka PG 285* potentiostat/galvanostat. Reactions were followed by GC-MS to determine when the end point had been reached.

6.1 Physical Data

^{1}H NMR-spectroscopy

Bruker DPX 400 (400 MHz)

The chemical shifts δ are given in ppm relative to an internal standard. Tetramethylsilane was used in deuterated chloroform. All coupling constants J are reported in Hertz. The multiplicity of a signal is designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = unresolved multiplet, br = broad. Signals that have not been assigned to a specific proton on an aromatic ring are labeled as aromatic.

^{13}C NMR-spectroscopy

Bruker DPX 400 (100 MHz)

The chemical shifts δ are given in ppm relative to the solvent signal of deuterated chloroform (δ = 77.0 t). Peaks were assigned based on DEPT (distortionless enhancement by polarisation transfer) sequences as required. Where conclusive assignment has not been possible, peaks are labled as to the number of carbons they represent.

^{77}Se NMR Spectroscopy

Jeol Eclipse 300 (57.3 MHz)

The chemical shifts are give in ppm relative to diphenyl diselenide (δ = 475 ppm)

Mass Spectrometry

Fisons VG Platform

The analyses were performed by Sham Ali in the mass spectrometry laboratory of the Chemistry Department, Cardiff University. Ions were generated using APCI (atmospheric pressure chemical ionisation). High Resolution mass spectrometry was carried out by the EPSRC mass spectrometry service at the University of Swansea.

Gas Chromatography Mass Spectrometry

Varian Saturn 3400 GC/MS

DB 5-MS 30 m column 0.5 mm inner diameter, helium at 12 psi used as the carrier gas. Injector was set to 230°C, detector at 250°C, ions were generated by Electronic Ionisation and detected in a *Varian Ultratrace* ion trap, column conditions varied between experiments.

IR-Spectroscopy

Perkin Elmer 1600 FTIR spectrometer

Wavenumbers quoted in cm^{-1}. All samples were measured as a liquid film on sodium chloride plates.

Optical Rotation

Measurments were carried out using an *Optical Activity Ltd. AA-1000* Polarimeter at a wavelength of 589 nm, cell length 5 cm, concentrations c given in g per 100 ml.

Chromatography

Thin layer chromatography was performed on *Merck silica gel 60 F254* precoated aluminium backed plates. The plates were visualised by ultraviolet-fluorescence or developed by iodine vapour or basic potassium permanganate solution in water.

Flash chromatography was carried out using *Fisher* silica gel 60 (35-70 mesh), the eluent is given for each product.

Medium pressure liquid chromatography was carried out using the *Buchi 681 solvent* delivery system, column diameter 2.5 cm, column length 40 cm, packed with *Merck silica gel LiChroprep Si 60* (15-25 μm), detected using a *Buchi UV/Vis-Filter-Photometer* and fractions collected with a *Bio-Rad Model 2128* fraction collector.

High performance liquid chromatography

a) *Merck-Hitachi L6200* gradient pump with *Merck-Hitachi L4200 UV/Vis* detector and *Merck-Hitachi L2500* integrator.
b) *Shimadzu LC-10AT-VP* solvent delivery system, *Shimadzu SPD-M10A-VP DAD* detector, *Shimadzu SCL-10A-VP* controller, *Shimadzu Class VP* software

The column used for all separations was the Chiracel OD-H, from Daicel Chemical industries column length 25 cm, diameter 4.6 mm. Solvent flow rate was maintained at 0.5 ml/min for all separations.

6.2 General Experimental Procedures

General procedure for the electrochemical reaction of diselenides with alkenes (**GP 1**)

The alkene (0.1 mmol) was dissolved in methanol (7 ml) or a water acetonitrile mixture (2ml and 5 ml) with the diselenide (0.01 mmol), tetraethyl ammonium bromide (0.1 mmol, 21 mg) and sulphuric acid (2 μl). The mixture was electrolysed under constant current for 4 hours before the solvent was removed under *vacuo*. Diethyl ether and water were added and the aqueous layer extracted with diethyl ether. The combined organic layers were dried over magnesium sulphate and the solvent removed. Purification by flash chromatography or preparative TLC gave the allylic ethers or allylic alcohols as clear oils.

General procedure for the reaction of selenium electrophiles with alkenes (**GP 2**)

The diselenide (0.1 mmol) or the methoxymethyl selenide (0.2 mmol) was dissolved in diethyl ether (4 ml), cooled to 0°C and treated with bromine (0.11 mmol, 0.11 ml of a 1 M solution in carbon tetrachloride). After stirring for 10 minutes silver triflate (72 mg, 0.28 mmol) in methanol (0.1 ml) was added. The reaction was cooled to –78°C and stirred for 10 minutes before the alkene was added. After stirring for 4 hours, *sym*-collidine was added followed by water. Extraction with diethyl ether, drying over magnesium sulphate and removal of the solvent gave the crude product. Purification was carried out by flash chromatography on silica gel.

General procedure for the synthesis of diselenides and methoxymethylselenides from bromo precursors (**GP 3**)

The bromo precursor (1 mmol) was dissolved in THF (10 ml), cooled to –78°C and treated with *t*-butyllithium (2.5 mmol for precursors containing a hydroxy group, 1.5 mmol of a 1.5 M solution in hexane, for all other precursors). After warming up to room temperature and stirring for 30 minutes, selenium (86 mg, 1.1 mmol) was added at 0°C. The reaction was stirred for a further 6 hours, treated with HCl, (1 M, 10 ml) and extracted with diethyl ether (3 x 20 ml). The organic layer was washed with water, dried over magnesium sulphate then treated with powdered potassium hydroxide (50 mg). The solvent was removed and the crude mixture purified by flash chromatography.

Alternative procedure for the synthesis of diselenides from bromo precursors (**GP 4**)

The bromo precursor (1 mmol) was dissolved in hexane (5 ml), cooled to –78°C and treated with *t*-butyllithium (2.5 mmol for precursors containing a hydroxy group, 1.5 mmol of a 1.5 M solution in hexane for all other precursors). After warming slowly to room temperature, the reaction was cooled to –78°C and treated with THF (5 ml). The reaction was warmed again to room temperature and stirred for 20 minutes before cooling to –78°C and adding selenium. The reaction was allowed to slowly warm to room temperature and stirred for 12 hours before HCl (10 ml) was added. Diethyl ether (10 ml) was added and the organic layer was washed with water before drying over magnesium sulphate. The solvent was removed and the product purified by flash chromatography.

General procedure for enantioselective reduction of acetophenones to the corresponding (*R*)-alcohols by (+)-DIP Cl (**GP 5**)[76]

The ketone (5 mmol) was dissolved in THF (2 ml) and added to a solution of chlorodiisopinocampheyl borane (1.63 g, 5.1 mmol in 5 ml THF) at –20°C and stirred for up to 48 hours until all the alcohol had been consumed. The THF was removed and the mixture dissolved in diethyl ether (10 ml) before diethanol amine (1.05 g, 10 mmol) was added dropwise with vigorous stirring. After 3 hours, the mixture was filtered through celite and the solvent removed. The product was purified by flash chromatography.

General procedure for the reduction of alcohols by sodium borohydride (**GP 6**)

The alcohol (1 mmol) was dissolved in methanol (10 ml), cooled to 0°C and treated with sodium borohydride (53 mg, 1.4 mmol). The reaction was warmed to room temperature and after stirring for 2 hours the methanol was removed. The mixture was dissolved in diethyl ether (10 ml), washed with water, and the organic layer dried over magnesium sulphate before the solvent was removed to give the pure alcohol.

General procedure for the synthesis of methoxymethyl selenides and selenides from alcohols (**GP 7**)

The alcohol (5 mmol) was dissolved in ethanol (15 ml), cooled to -20°C, treated with potassium hydroxide (560 mg, 10 mmol) and tosyl chloride (980 mg, 5 mmol) then

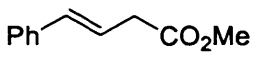
stirred for 24 hours. In a separate flask, methoxymethyl diselenide (662mg, 2.5 mmol) or the diselenide (2.5 mmol) was dissolved in ethanol (10ml) and treated with sodium borohydride (190 mg, 5 mmol). The resulting clear solution was added to the tosylate and the mixture stirred for 24 hours. The reaction was quenched with water, diethyl ether (20 ml) added and the organic layer washed with saturated sodium chloride solution before drying over magnesium sulphate. The solvent was removed and the product purified by flash chromatography or by preparative thin layer chromatography.

General procedure for the oxidative elimination of selenides to alkenes (**GP 8**)

The selenide (1 mmol) was dissolved in a methanol/water mixture (10 ml, 9:1) and ammonium peroxydisulphate (678 mg, 3 mmol) added. The reaction was stirred at room temperature for 18 hrs, before diethyl ether (20 ml) was added. The organic layer was separated from the aqueous layer and the aqueous layer extracted with diethyl ether (3 x 20 ml). The combined organic layers were dried over magnesium sulphate and the solvent removed. The alkenes were purified by flash chromatography.

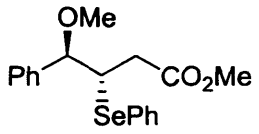
6.3 Compound Data

Methyl-(*E*) 4-Phenylbut-3-enoate **27**



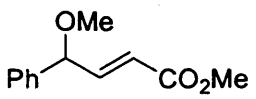
Synthesised from malonic acid and phenyl acetaldehyde with subsequent esterification according to the literature procedure.[77] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 3.20 (2 H, d, J = 6.0, CH_2), 3.68 (1 H, s, OCH_3), 6.19 (1 H, dt, J = 16.1 , J = 6.0, =C*H*R), 6.50 (1 H, d, J = 16.1, =C*H*Ar), 7.2-7.4 (5 H, m, Ar-*H*).

4-Methoxy-4-phenyl-3-phenylselanyl-butyric acid methyl ester **28**



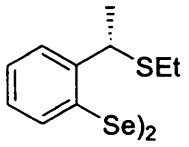
Prepared from **27** and phenylselenenyl bromide by **GP 2**. Purification by flash chromatography (eluent 9:1 petrol:diethyl ether) to give **28** as a clear oil (41 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 2.65 (1 H, dd, J = 16.3, J = 5.7, C*H*H), 2.84 (1 H, dd, J = 16.4, J = 8.3, CH*H*), 3.16 (3 H, s, OCH_3), 3.48 (3 H, s, OCH_3), 3.65 (1 H, ddd, J = 8.3, J = 6.2, J = 5.7, C*H*Se), 4.28 (1 H, d, J = 6.2, PhC*H*), 7.13-7.24 (8 H, m, Ar-*H*), 7.36 (2 H, dd, J = 7.6, J = 1.7, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 36.6 (CH_2), 46.7 (*C*HSe), 51.6 (OCH_3), 57.4 (OCH_3), 85.8 (Ph*C*H), 127.3 (2 C), 127.7 (1 C), 128.1 (1 C), 128.3 (2 C), 128.9 (2 C), 129.2 (1 C), 134.9 (2 C), 139.0 (1 C), 172.4 (*C*O); IR (NaCl): υ = 2821, 1736, 1578, 1436, 1209, 1092, 1022, 741, 701 cm^{-1}; *m/z* (intensity) 364 (6%) [M$^+$], 207 (9%), 206 (8%), 157 (8%), 147 (7%), 122 (8%), 121 (100%), 117 (13%), 115 (16%), 105 (6%), 91 (25%), 77 (27%), 51 (10%), 41 (7%); HRMS for $C_{18}H_{20}O_3Se$: calcd 364.0572, found 364.0583.

(*E*)-4-Methoxy-4-phenyl-but-2-enoic acid methyl ester **30**[78]



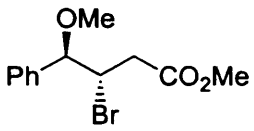
Synthesised from **27** by **GP 1**. Purified by preparative TLC (eluent 9:1 petroleum ether:diethyl ether) to give 30 as a clear oil (19 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 3.32 (3 H, s, OCH_3), 3.71 (3 H, s, CO_2CH_3), 4.48 (1 H, dd, J = 5.5, J = 1.6, $CHOCH_3$), 6.10 (1 H, dd, J = 15.7, J = 1.6, CH=$CHCO_2$), 6.95 (1 H, dd, J = 15.7, J = 5.5, CH=$CHCO_2$), 7.25-7.4 (5 H, m, Ar-*H*). Separation of enantiomers by HPLC (eluent 98:2 hexane:isopropanol), R_f(*S*)=21.6 min, R_f (*R*)=24.2 min. Absolute stereochemistry assigned by comparison with literature.[29]

(*R,R*)-Bis-[2-(1-ethylsulphanyl)-ethylphenyl] diselenide **39**



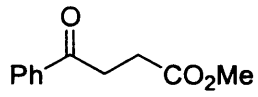
Synthesised from **59** and sodium ethanethiolate by **GP 4**. Purification by flash chromatography gave **39** as a red oil (60 mg, 72% yield). $[\alpha]_D$ = - 18.0 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.10 (3 H, t, J = 7.6, CH_2CH_3), 1.46 (3 H, d, J = 6.8, CHC_3), 2.34 (2 H, dq, J = 7.6, J = 2.8, SCH_2), 4.37 (1 H, q, J = 7.2, CHS), 7.04 (1 H, dt, J = 7.6, J = 1.2, Ar-*H*), 7.17 (1 H, m, Ar-*H*), 7.35 (1 H, dd, J = 8, J = 1.2, Ar-*H*), 7.68 (1 H, dd, J = 8, J = 1.2, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 15.0 (CH_2CH_3), 22.0 (CH_2CH_3), 25.7 ($CHCH_3$), 43.7 (CH), 127.4 (Ar), 128.2 (Ar), 128.6 (Ar), 132.4 (Ar), 134.5 (Ar), 144.9 (Ar); Se^{77} NMR (95 MHz, $CDCl_3$):δ = 430.2; IR (NaCl): υ = 3056, 2965, 2915, 1719, 1579, 1463, 1373, 1262, 1021, 755, 730 cm^{-1}.

4-Methoxy-4-phenyl-3-bromobutyric acid methyl ester **31**



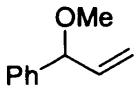
Synthesised from **27** by **GP 1**. Purification by preparative TLC (eluent 9:1 petrol:diethyl ether) to give **39** as a clear oil (12 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 2.82 (1 H, dd, J = 16.5, J = 9.3, CH*H*), 2.99 (1 H, dd, J = 16.5, J = 3.76, C*H*H), 3.23 (3 H, s, CHOCH_3), 3.61 (3 H, s, OCH_3),4.34-4.44 (2 H, m, C*H*C*H*), 7.28-7.37 (5 H, m, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 31.7 (*C*H_2), 36.4 (*C*HBr), 51.2 (O*C*H_3), 57.7 (O*C*H_3), 83.9 (Ar*C*H), 124.9 (1 C), 127.1 (2 C), 127.8 (2 C) 136.4 (1 C); IR (NaCl): υ = 2994, 1741, 1482, 1238, 1171, 1077, 1001, 996 cm^{-1}; *m/z* (intensity) 287 (12%) [M$^+$], 257 (24%) 255 (22%) 224 (32%) 209 (51%) 194 (100%), 177 (82%), 121 (38%), 98 (42%), 84 (26%); HRMS for $C_{12}H_{15}BrO_3$: calcd 287.0277, found 287.0273.

4-Oxo-4-phenyl butyric acid methyl ester **42**[62]



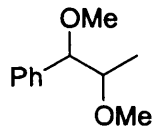
Synthesised from **27** by **GP 1**.[79] Purification by preparative TLC (eluent 9:1 petrol:diethyl ether) to give 42 as a clear oil (8 mg, 43 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72 (2 H, d, J = 6.8, $CH_2CH_2CO_2$), 3.36 (2 H, d, J = 6.8, $CH_2CH_2CO_2$), 3.58 (3 H, s, OCH_3), 7.10-7.53 (4 H, m, Ar-*H*), 7.95 (2 H, dd, J = 8.2, J = 1.7, Ar-*H*).

(1-methoxy-allyl)-benzene (racemate) **44**[80]



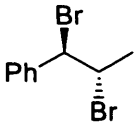
Synthesised from β-methyl styrene by **GP 1**. Purification by preparative TLC (eluent 15:1 petrol:diethyl ether) to give **44** as a clear oil (9 mg, 54 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.25 (3 H, s, OC*H*$_3$), 4.55, (1 H, d, *J* = 6.7, PhC*H*), 5.17 (1 H, dd, *J* = 16.2, *J* = 1.8, =CH*H*), 5.23 (1 H, dd, *J* = 8.0, *J* = 1.8, =C*H*H), 5.86 (1 H, m, =C*H*), 7.10-7.38 (5 H, m, =Ar-*H*). Separation of enantiomers by chiral GC. Column Varian CP Chiralsil-DEX CB, 0.25 mm diameter 25 m length, 15 psi, 70°C. R_f(*R*):43.1 min, R_f(*S*), 44.5 min.[81]

1,2-Dimethoxy-1-phenylpropane **45**[82]



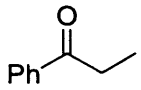
Synthesised from β-methyl styrene by **GP 1**. Purified by preparative TLC (eluent 20:1 petroleum ether:diethyl ether) to give **45** as a clear oil (12 mg, 68 % yield, *syn*:*anti* 2:3). ^{1}H NMR (400 MHz, $CDCl_3$): *syn*: δ = 1.15 (3 H, d, *J* = 6.3, C*H*$_3$), 3.35, (6 H, s, 2xC*H*$_3$), 3.45 (1 H, dq, *J* = 6.32, *J* = 4.80, C*H*CH$_3$), 4.20 (1 H, d, *J* = 4.8, C*H*Ph), 7.35 (5 H, m, Ar-*H*); *anti*: 0.9 (3 H, d, *J* = 6.9, C*H*$_3$), 3.25 (3 H, s, OC*H*$_3$), 3.45 (3 H, s, OC*H*$_3$), 3.55 (1 H, q, *J* = 6.9, C*H*CH$_3$), 4.1 (1 H, d, *J* = 6.9, C*H*Ph), 7.2-7.45 (5 H, m, Ar-*H*).

1,2-Dibromo-1-phenylpropane **46**[83]



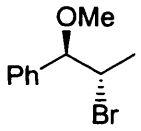
Synthesised from β-methyl styrene by **GP 1**. Purification by preparative TLC (eluent petrol) to give **46** as a clear oil (15 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.98 (3 H, d, J = 6.8, CH_3), 2.0 (1 H, dd, J = 6.8, J = 10.5, $CHCH_3$), 4.95 (1 H, d, J = 10.5, PhC*H*), 7.01-7.04 (5 H, m, Ar-*H*).

Propiophenone **47**[84]



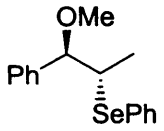
Synthesised from β-methyl styrene by **GP 1**. Purification by preparative TLC (eluent petrol) to give **47** as a clear oil (9 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (3 H, t, J = 6.9, CH_3), 2.98 (2 H, q, J = 6.9, CH_2), 7.28-7.68 (3 H, m, Ar-*H*), 7.95 (2 H, m, Ar-*H*).

2-Bromo-1-methoxy-1-phenyl propane **48**[85]



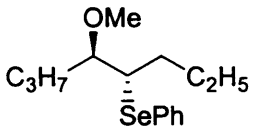
Synthesised from β-methylstyrene by **GP 1**. Purification by preparative TLC (eluent 20:1 petroleum ether:diethyl ether) to give **48** as a clear oil (15 mg, 65% yield).. ^{1}H NMR (400 MHz, $CDCl_3$):1.86 (3 H, d, J = 7.2, CH_3), 3.41, (3 H, s, OCH_3), 3.57 (dd, J = 9.5, J = 7.1, C*H*Br), 4.23 (1 H, d, J = 9.5, $CHOCH_3$), 7.05-7.44 (5 H, m, Ar-*H*).

1-Methoxy-2-phenylselanyl-1-phenylpropane **49**[86]



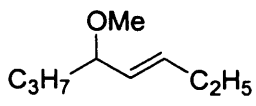
Synthesised from β-methylstyrene by **GP 2**. Purification by preparative TLC (eluent 10:1 petroleum ether:diethyl ether) to give **48** as a clear oil (42 mg, 57% yield). 1.25 (3 H, d, J = 6.8, CHCH_3), 3.18 (3 H, s, OCH_3), 3.34, (1 H, m, CHSe), 4.38 (1 H, d, 6.7, CHOCH$_3$), 7.10-7.32 (8 H, m, Ar-H), 7.46 (2 H, m, Ar-H).

5-Methoxy-4-phenylselenyl-octane **50**



Synthesised from *trans*-4-octene by **GP 2**. Purified by flash chromatography (eluent 20:1 petrol:diethylether) to give **50** as a clear oil (95 mg, 81% yield).^{1}H NMR (400 MHz, $CDCl_3$):δ = 0.84 (6 H, m, 2xCH_3), 1.20-1.61 (8 H, m, 2xCH_2CH_2), 3.19-3.25 (2 H, m, 2xCH), 3.26 (3 H, s, OCH_3), 7.17-7.19 (3 H, m, Ar-H), 7.50-7.57 (2 H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 14.4 (*C*H$_3$), 14.6 (*C*H$_3$), 19.5 (*C*H$_2$), 21.9 (*C*H$_2$), 34.2 (*C*H$_2$), 34.4 (*C*H$_2$), 51.1 (*C*H), 58.4 (*C*H), 84.3 (O*C*H$_3$), 127.5 (1 C), 129.2 (2 C), 130.4 (1 C), 134.9 (2 C); IR (NaCl): υ = 2956, 1463, 1092, 735, 690 cm^{-1}; *m/z* (intensity): 300 (100%) [M$^+$], 143 (82%), 111 (12%); HRMS for $C_{15}H_{24}OSe \bullet NH_4$: calcd 318.1331, found 318.1333.

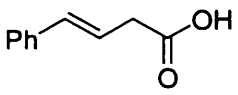
(*E*)-5-Methoxy-3-octene **51**[87]



Synthesised from **50** by **GP 8**. Purified by flash chromatography (eluent petrol) to give **51** as a clear oil (73 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83-1.21 (6 H,

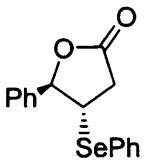
m, 2xCH_2CH_3), 1.26-1.84 (4 H, m, CH_2CH_3), 1.9-2.2 (2 H, m,), 3.28 (3 H, s, OCH_3), 3.40, (1 H, m, $CHOCH_3$), 5.20 (1 H, ddt, J = 16.2, J = 8.0, J = 1.9, =CHC_2H_5), 5.60 (1 H, dt, J = 16.2, J = 5.0, =$CHCHOCH_3$).

(*E*)-4-Phenyl-3-butenoic acid **53**[53]



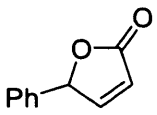
Synthesised from malonic acid and phenyl acetaldehyde by a Knoevenagle type condensation following a literature procedure to give **53** as a white solid (1.3 g, 92 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.22 (2 H, d, J = 5.9, CH_2), 6.20 (1 H, m, PhCH=C*H*R), 6.45 (1 H, d, J = 15.9, PhC*H*), 7.05-7.4 (5 H, m, Ar-*H*).

5-Phenyl-4-phenylselanyl-dihydrofuran-2-one **54**



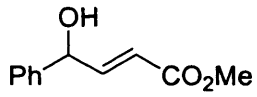
Prepared from 4-phenyl butyric acid by **GP 2**. Purification by flash chromatography (eluent 20:1 petroleum ether:ethyl acetate) to give **54** as a clear oil (55 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 2.55-2.64 (m, 1 H, C*H*H), 2.93-2.99 (m, 1 H, CH*H*), 3.64-3.70 (1 H, m, SeC*H*), 5.30 (1 H, d, J = 6.9, PhC*H*), 7.20-7.4 (9 H, m, Ar-*H*), 7.46 (1 H, d, J = 8.0, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ =36.3 (CH_2), 42.6 (*C*HSe), 85.5 (Ph*C*H), 126.1 (2 C), 126.2 (1 C), 129.2 (2 C), 129.3 (1 C), 129.5 (1 C), 129.9 (2 C), 136.5 (2 C), 137.6 (1 C), 175.0 (CO_2); IR (NaCl): υ = 3057, 2356, 1783, 1477, 1437, 1256, 1202, 1138, 999, 865, 741, 695 cm^{-1}; *m/z* (intensity): 319 (41%), 272 (76%), 160 (65%), 82 (55%), 79.2 (100%); HRMS for $C_{16}H_{14}O_2Se$: calcd 319.0237, found 319.0239.

5-Phenylfuran-2-one **55**[88]



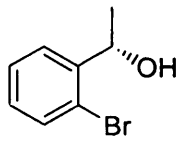
Synthesised from **54** by GP **8**. Purified by flash chromatography (eluent petroleum ether) to give **55** as a clear oil (11 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 6.02 (dd, 1 H, J = 2.1, J = 1.9, PhCH=C*H*), 6.22 (1 H, dd, J = 5.6, J = 2.1, PhC*H*=CH), 7.25-7.29 (2 H, m, Ar-*H*), 7.37-7.54 (3 H, m Ar-*H*,), 7.54 (1 H, dd, J =5.6, J = 1.9, Ar-*H*)

4-Hydroxyl-4-phenylbutyric acid methyl ester **56**[89]



Synthesised from **27** by **GP 1**. Purified by preparative TLC (eluent 5:1 petroleum ether:diethyl ether) to give **56** as a clear oil (5 mg, 24% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.0 (1 H, br, s, O*H*), 3.71 (3 H, s, OCH_3), 5.36 (1 H, dd, J = 4.8, J = 1.8, PhC*H*), 6.18 (1 H, dd, J = 15.6, J = 1.8, C*H*=$CHCO_2$), 7.03 (1 H, dd, J = 15.6, J = 4.8, =C*H*CO_2), 7.2-7.4 (5 H, m, Ar-*H*).

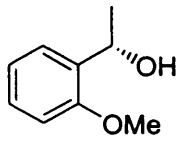
(*S*)-2-(2-Bromophenyl) ethanol **59a**[90]



Synthesised from 2-bromoacetopheneone by **GP 5**. Purified by flash chromatography (eluent 4:1 petrol:diethyl ether) to give **59a** as a clear oil (4.6 g, 89% yield, 96% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (3 H, d, J = 6.3, CH_3), 5.18 (1 H, q, J = 6.3, C*H*),

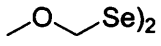
6.98 1 H, dt, J = 7.7, J = 1.6, Ar-*H*), 7.28 (1 H, dt, J = 7.4, J = 1.1, Ar-*H*), 7.42 (1 H, dd, J = 7.9, J = 1.2, Ar-*H*), 7.51 (1 H, dd, J = 7.9, J = 1.7, Ar-*H*).

(*S*)-2-(2-Methoxyphenyl) ethanol **59b**[91]



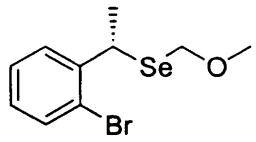
Synthesised from 2-methoxyacetopheneone by **GP 5**. Purified by flash chromatography (eluent 3:1 petrol:diethyl ether) to give **59b** as a clear oil (5.5 g, 94% yield, 96% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (3 H, d, J = 6.7, CH_3), 3.79 (3 H, s, OCH_3), 5.00 (1 H, q, J = 6.7, C*H*), 6.78 (1 H, d, J = 8.1, Ar-*H*), 6.91 (1 H, t, J = 7.9, Ar-*H*), 7.18 (1 H, m, Ar-*H*), 7.25 (1 H, d, J = 7.9, Ar-*H*).

Dimethoxymethyl diselenide **61**[92]



Synthesised from disodium diselenide and methoxymethyl chloride according to the literature procedure in 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.04 (6 H, s, CH_3), 5.31, (4 H, s, CH_2).

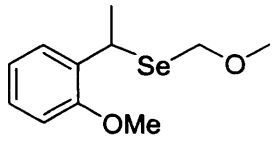
(*S*)-1-Bromo-2-(1-methoxymethylselanyl-ethyl)-benzene **63a**



Synthesised from **59a** and **61** by **GP 7**. Purification by preparative TLC (eluent 4:1 petroleum ether:diethyl ether) to give **63a** as an orange oil (4 mg, 15% yield). $[\alpha]_D$ =

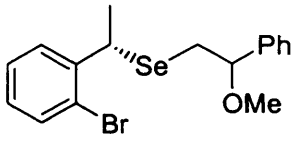
+83.2 (c = 0.4 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$):δ = 1.72 (3 H, d, J = 7.2, $CHCH_3$), 3.24 (3 H, s, OCH_3), 4.69 (1 H, q, J = 7.2, C*H*), 4.84, (1 H, d, J = 10.0, C*H*H), 4.90, (1 H, d, J = 10.0, CH*H*), 7.00 (1 H, dt J = 7.2, J = 1.5, Ar-*H*), 7.23 (1 H, t, J = 7.6, Ar-*H*), 7.45 (2 H, m, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 23.2 (CH_3), 36.6 (*C*H), 57.2 (OCH_3), 71.1 (CH_2), 124.0 (1 C), 128.1 (1 C), 128.5 (1 C), 129.0 (1 C), 133.3 (1 C), 143.7 (1 C); IR (NaCl) υ = 2916, 1444, 1271, 1179, 1082, 1021, 925, 871, 756 cm^{-1}; *m/z* (intensity): 308 (15%) [M^+], 277 (8%), 185 (99%), 183 (100%), 104 (71%), 77 (34%), 45 (73%); HRMS for $C_{10}H_{13}BrOSe{\bullet}NH_4$: calcd 325.9653, found 325.9649.

1-Methoxy-2-(1-methoxymethylselanyl-ethyl)-benzene (racemate) **63b**



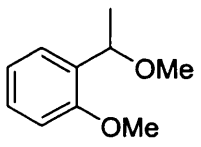
Prepared from 1-(1-Bromo-ethyl)-2-methoxy-benzene by **GP 7**. Purification by flash chromatography (eluent 9:1 petroleum ether:diethyl ether) to give **63b** as a clear oil (81 mg, 69% yield). ^1H NMR (400 MHz, $CDCl_3$):δ = 1.81 (3 H, d, J = 7.2, $CHCH_3$), 3.32 (3 H, s, CH_2OCH_3), 3.88 (3 H, s, $ArOCH_3$), 4.76 (1 H, q, J = 7.2, C*H*), 4.94 (2 H, s, CH_2), 6.88 (1 H, d, J = 8.1, Ar-*H*), 6.96 (1 H, t, J = 7.48, Ar-*H*), 7.22 (1 H, dt, J = 7.79, J = 1.6, Ar-*H*), 7.39 (1 H, dd, J = 7.6, J = 1.51, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 22.9 ($CHCH_3$), 30.9 (*C*H), 55.9 (OCH_3), 57.1 (OCH_3), 71.1 (CH_2), 111.1 (1 C), 121.1 (1 C), 127.9 (1 C), 128.1 (1 C), 133.1 (1 C), 156.5 (1 C); IR (NaCl) υ =3378, 2922, 1597, 1490, 1462, 1244, 1178, 1081, 1026, 922, 751 cm^{-1}; *m/z* (intensity): 260 (100%), 215 (21%), 199 (38%), 185 (49%), 157 (66%), 149 (79%); HRMS for $C_{11}H_{16}O_2Se$: calcd 260.0310, found 260.0312.

1-Bromo-2-[1-(*S*)-(2-methoxy-ethylbenzylselanyl)-ethyl]-benzene **64a** (mixture of diastereomers)



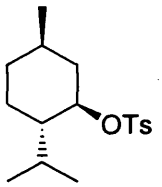
Prepared from styrene and **63a** by **GP 2**, Purification by flash chromatography (eluent 9:1 petroleum ether:diethyl ether) to give **64a** as a clear oil (25 mg, 70% yield, 0% *de*). $[\alpha]_D$ = +52.6 (c = 0.7 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.60 (3 H, d, J = 7.0, CHC*H*$_3$), 1.61 (3 H, d, J = 7.1, CHC*H*$_3$), 2.59 (2 H, m, SeC*H*$_2$), 2.83 (2 H, m, SeC*H*$_2$), 3.98 (1 H, dd, J = 5.0, J = 3.94, C*H*OMe), 4.14 (1 H, dd J = 5.1, J = 3.5, C*H*OMe), 4.64 (1 H, q, J = 7.0, C*H*CH$_3$), 4.71 (1 H, q, J = 7.1, C*H*CH$_3$), 6.96 (4 H, m, Ar-*H*), 7.20 (8 H, m, Ar-*H*), 7.47 (6 H, m, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 22.8 (*C*H$_3$), 22.9 (*C*H$_3$), 31.6 (*C*HSe), 32.0 (*C*HSe), 36.3 (*C*H$_2$Se), 36.7 (*C*H$_2$Se), 57.3 (*C*H$_3$O), 57.4 (*C*H$_3$O), 83.8 (Ph*C*H), 84.1 (Ph*C*H), 123.6 (1 C), 126.9 (2 C), 128.1 (1 C), 128.3 (1 C), 128.4 (1 C), 128.5 (1 C), 128.8 (2 C), 129.3 (1 C), 133.1 (1 C), 142.2 (1 C); IR (NaCl) υ =3281, 2954, 1608, 1321, 1210, 1168, 881 cm^{-1}; *m/z* (intensity): 398 (5%) [M$^+$], 367 (3%), 287 (2%), 183 (10%), 121 (100%), 104 (18%), 91 (6%), 77 (10%); HRMS for $C_{17}H_{19}BrOSe$: calcd 397.9779, found 397.9777.

1-Methoxy-2-(1-methoxyethyl)-benzene **67**[93]



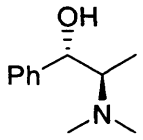
Synthesised from **63b** by **GP 7**. Purified by flash chromatography (eluent 20:1 petroleum ether:diethyl ether) to give **67** as a clear oil (77 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (3 H, d, J = 6.4, C*H*), 3.28 (3 H, s, CHOC*H*$_3$), 3.85 (3 H, s, ArOC*H*$_3$), 4.78 (1 H, q, J = 6.4, C*H*), 6.98-7.42, (4 H, m, Ar-*H*).

(-)-Menthyl-toluenesulphonate **68**[94]



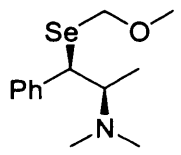
(-)-Menthol (1 g, 6.4 mmol) was dissolved in pyridine (3ml), tosyl chloride (1.75 g, 8.9 mmol) added and the reaction stirred at room temperature overnight. The crystals were filtered off and the traces of pyridine removed by 3 hours at reduced pressure (10^{-2} mbar) to give **68** as a white crystalline solid (1.44 g, 73%, mpt 91.4-92.4°C (lit 92.3-93.0°C).

(*R*,*R*)-*N*,*N*-Dimethylnorephedrine **70**



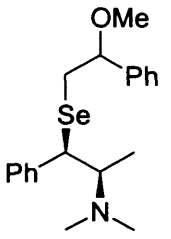
(*R*,*R*)-Norephedrine (200 mg, 1.29 mmol) was dissolved in formic acid (552 mg, 12 mmol) and formaldehyde (630 μl, 7.8 mmol of a 30% solution in water) and refluxed for 14 hours. The solution was cooled and sodium hydroxide added until the solution was pH 10. The product was extracted into diethyl ether, washed with saturated ammonium chloride solution, dried over magnesium sulphate and the solvent removed to give **70** as a white crystalline solid (230 mg, 93%, mpt 86.4-87.0°C, lit. 87.5-88.2°C).[95]

(*S*,*R*)-(2-Methoxymethylselanyl-1-methyl-2-phenyl-ethyl)-dimethyl-amine **71**



Synthesised from **70** and dimethoxymethyl diselenide by **GP 7**. Purified by preparative TLC (eluent 1:1 petrol:diethyl ether) to give **71** as a red oil (4 mg, 9% yield). $[\alpha]_D$ = -228.9 (c = 0.5 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$):δ =1.17 (3 H, d, J = 7.0, $CHCH_3$), 2.10 (6 H, s, $N(CH_3)_2$), 3.05 (1 H, m, CHN), 3.21 (3 H, s, OCH_3), 4.17 (1 H, d, J = 9.0, CHSe), 4.52 (1 H, d, J = 9.9, SeCHH), 4.58 (1 H, d, J = 9.9, SeCHH), 7.15 (1 H, dt, J = 6.8, J = 1.8, Ar-H), 7.21-7.27 (4 H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 12.0 ($CHCH_3$), 40.6 ($N(CH_3)_2$), 47.8 (PhCH), 56.9 (OCH_3), 63.1 ($CHCH_3$), 70.0 (OCH_2), 126.6 (1 C, Ar), 128.1 (2 C, Ar), 128.7 (2 C, Ar), 142.2 (1 C, Ar); IR (NaCl): υ = 2924, 1452, 1264, 1178, 1082, 926, 698 cm^{-1}; *m/z* (intensity) 288 (8%) [M^+], 286 (6%), 163 (6%), 163 (6%), 162 (60%), 72 (100%); HRMS for $C_{13}H_{21}NOSe$: calcd 288.0861, found 288.0860.

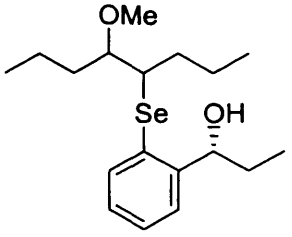
(*S*,*R*)-(2-(2-Methoxy-2-phenylethyl)-selanyl-1-methyl-2-phenyl-ethyl)-dimethyl-amine **73**



Synthesised from **71** and styrene by **GP 2**. Purification preparative TLC (eluent 20:1 petroleum ether:diethyl ether) to give **73** as a clear oil (3 mg, 17% yield, 0% *de*). ^1H NMR (400 MHz, $CDCl_3$):δ = 1.15 (3 H, d, J = 7.0, CH_3), 1.21 (3 H, d, J = 6.6, CH_3), 2.17 (6 H, s, $N(CH_3)_2$), 2.23 (6 H, s, $N(CH_3)_2$), 2.34 (1 H, m, CHHSe), 2.37 (1 H, m, CHHSe), 2.60, (2 H, m, 2xCHHSe), 2.95 (1 H, m, CHN), 3.08 (3 H, s, OMe), 3.09 (3 H, s, OMe), 3.14 (1 H, m, CHN), 3.89 (2 H, m, PhCHOMe and PhCHSe), 4.02 (1 H, t, J = 6.65, PhCHOMe), 4.10 (1 H, d, J = 8.3, PhCHSe), 7.05-7.31 (20 H, Ar-H). Diastereomeric excess determined by integration of peaks at 3.08 and 3.09 ppm.

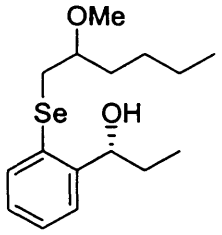
Compounds **74**[96], **76**[97], **77**[47], **78**[98] synthesised by literature methods.

(*S*)-1-[2-(2-Methoxy-1-propyl-pentylselanyl)-phenyl]-propan-1-ol **81** (mixture of diastereoisomers)



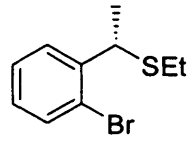
Prepared from *trans*-4-octene and diselenide **37** by **GP 2**. Purification by flash chromatography (eluent 4:1 petroleum ether:ethyl acetate) to give **81** as a clear oil, (22 mg, 54% yield, 20% *de*). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 0.78-0.93 (18 H, m C*H*$_3$x6), 1.19-1.64 (16 H, 4xC*H*$_2$C*H*$_2$), 1.72 (2 H, quin, *J* = 7.1, C*H*$_2$CHOH), 1.92 (2 H, *J* = 7.0, C*H*$_2$CHOH), 2.71 (3 H, s, OC*H*$_3$), 3.28 (3 H, s, OC*H*$_3$), 5.05, 3.30 (1 H, t, *J* = 7.0, PhC*H*), 5.27 (1 H, t, *J* = 7.1, PhC*H*), 7.09 (2 H, m, Ar-*H*), 7.23 (2 H, m, Ar-*H*), 7.37 (1 H, d, *J* = 7.9, Ar-*H*), 7.38, (1 H, d, *J* = 7.7, Ar-*H*), ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 9.4 (1 C), 9.5 (1 C), 12.9 (1 C), 13.1 (1 C), 18.2 (1 C), 18.3 (1 C), 20.5 (1 C), 20.8 (1 C), 32.1 (1 C), 32.8 (1 C), 33.1 (1 C), 33.2 (1 C), 33.7 (1 C), 51.2 (1 C), 51.9 (1 C), 55.4 (1 C), 56.8 (1 C), 73.3 (1 C), 74.0, (1 C), 82.8 (1 C), 83.9 (1 C), 125.2 (1 C), 125.5 (1 C), 126.9 (1 C), 127.3 (1 C), 134.1 (1 C), 135.5 (1 C), 145.5 (1 C), 146.2 (1 C); IR (NaCl) υ = 3407, 3052, 2957, 2871, 2363, 1586, 1462, 1378, 1258, 1191, 1089, 975, 901, 824, 753 cm^{-1}; *m/z* (intensity): 357 (100%) [M$^+$], 341 (28%), 309 (18%), 197 (9%), 143 (95%), 111 (22%); HRMS for $C_{18}H_{28}O_2Se$: calcd 357.1327, found 357.1326.

(*S*)-1-[2-(2-methoxy-hexylselanyl)-phenyl]-propan-1-ol **82** (major diasteroisomer)



Prepared from 1-hexene and **37** by **GP 2**. Purification by flash chromatography (eluent 6:1 petroleum ether:ethyl acetate) to give **82** as a clear oil, (25 mg, 62% yield, 55% *de*). $[\alpha]_D$ = -44.2 (c = 1.4 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$):δ = 0.88 (3 H, t, *J* = 6.6, $CH_2CH_2CH_3$), 0.92 (3 H, t, *J* = 7.9, $CHCH_2CH_3$), 1.41 (4 H, m, CH_2CH_2), 1.62 (2 H, m, CH_2CHOCH_3), 1.88 (2 H, q, *J* = 7.9, CH_2CHOH), 2.95 3.24 (3 H, s, OCH_3), 3.36 (1 H, m, $CHOCH_3$), 5.05 (1 H, t, *J* = 6.5, ArC*H*), 7.11 (1 H, t, *J* = 7.4, Ar-*H*), 7.23 (1 H, t, *J* = 6.0, Ar-*H*), 7.41 (1 H, d, *J* = 6.0, Ar-*H*), 7.51 (1 H, d, *J* = 7.7, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 10.8 ($CH_2CH_2CH_3$), 14.4 (CH_2CH_3), 23.1 (CH_2CH_2), 27.8 ($CHCH_2$), 31.5 (CH_2CH_2), 33.0, 33.9 ($SeCH_2$), 56.9 (OCH_3), 74.9 (ArCH), 80.6 ($CHOCH_3$), 124.1 (1 C), 126.7 (1 C), 127.8 (1 C), 128.3 (1 C), 133.7 (1 C), 143.5 (1 C); IR (NaCl): υ = 3377, 2929, 2674, 2353, 1633, 1461, 1393, 1261, 1092, 802, 750 cm^{-1}; *m/z* (intensity) 330 (6%) [M^+], 281 (5%), 214 (15%), 197 (18%), 185 (16%), 164 (10%), 135 (100%), 101 (21%), 91 (12%), 77 (20%), 69 (80%); HRMS for $C_{16}H_{26}O_2Se$: calcd 330.1093, found 330.1090.

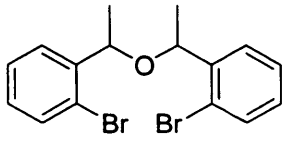
(*S*)-1-Bromo-2-(1-ethylsulphanyl-ethyl)-benzene **82**



Prepared from **59a** and sodiumethylsulphide by a literature procedure. Purified by flash chromatography to give **82** as a clear oil (212 mg, 52% yield). $[\alpha]_D$ = -54.7 (c = 1 in $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$):δ =1.22 (3 H, t, *J* = 7.6, CH_2CH_3), 1.44 (3 H, d, *J* = 6.8, $CHCH_3$), 2.31 (2 H, m, CH_2S), 4.50 (1 H, q, *J* = 6.8, $CHCH_3$), 7.01 (1 H, dt, *J* = 7.6, Ar-*H*), 7.25 (1 H, dt, *J* = 7.6, *J* = 0.8, Ar-*H*), 7.44 (1 H, d, *J* = 8.0, Ar-*H*), 7.55 (1 H,

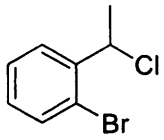
dt, J = 7.6, J = 1.6, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 15.0 (CH_2CH_3), 22.6 ($CHCH_3$), 25.7 (CH_2), 42.5 (*C*H), 124.2 (Ar), 128.3 (Ar), 128.7 (Ar), 129.1 (Ar), 132.9 (Ar), 143.6 (Ar); IR (NaCl) υ = 2970, 2924, 2360, 1467, 1438, 1372, 1263, 1021, 755, 726, 658 cm^{-1}; *m/z* (intensity): 245 (51%) [M$^+$], 183 (87%), 165 (23%), 135 (12%), 104 (100%), 77 (30%), 59 (7%); HRMS for $C_{10}H_{13}BrS$: calcd 243.9916, found 243.9912.

1-1(Oxydiethyliden)bis(2-bromobenzol) (racemate) **86**



2-(2-Bromophenyl) ethanol **59a** (132 mg, 0.66 mmol) was dissolved in pyridine (52 mg, 0.66 mmol), cooled to –40°C and treated with triflic anhydride (186 mg, 0.66 mmol). In a separate flask diphenyl diselenide (155 mg, 0.49 mmol) was dissolved in ethanol, cooled to 0°C and treated with sodium borohydride (22 mg, 0.58 mmol). This solution was stirred for 5 minutes before being added dropwise to the triflate solution, which was then allowed to warm slowly to room temperature. After 40 minutes stirring at room temperature, the reaction was quenched with water and the product extracted into diethyl ether, dried over magnesium sulphate and the solvent removed. Purification by flash chromatography (eluent 20:1 petroleum ether:diethyl ether) gave **86** as a clear oil. (159 mg, 64% yield, *erythro*:*threo* 1:1). Spectroscopic data consistent with published data.[99]

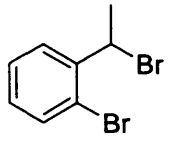
2-(2-Bromophenyl)chloroethane **87**



2-(2-Bromophenyl)ethanol (50 mg, 0.25 mmol) was dissolved in hexane (3 ml) and pyridine (1 ml), cooled to 0°C and treated with phosphorous oxychloride (38 mg, 0.25

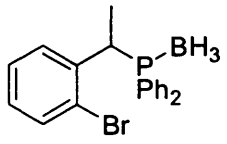
mmol). The reaction was allowed to warm to room temperature and stirred for 3 hours before water and diethyl ether were added. The organic layer was separated from the aqueous layer, dried over magnesium sulphate and the solvent removed to give **87** as a clean white solid (42 mg, 78%). Spectroscopic data consistent with published data.[100]

2-(2-Bromophenyl)bromoethane **88**[101]



2-(2-Bromophenyl)ethanol (1 g, 4.9 mmol) was dissolved in diethyl ether, cooled to 0°C and treated with phosphorous tribromide (0.89 g, 3.32 mmol). The reaction was allowed to warm slowly to room temperature and after stirring for 2 hours, water was added. The product was extracted into diethyl ether, washed with 5% sodium carbonate then saturated ammonium chloride and the solvent removed to give **88** as a clean clear oil (1.28 g, 86% yield). 1.95 (3 H, d, J = 7.0, CH_3), 5.84 (1 H, q, J = 7.0, CH), 6.8,

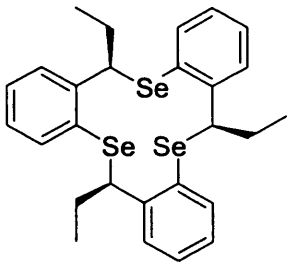
2-(2-Bromophenyl)-diphenylphosphine-ethane borane complex **90**



A modified literature procedure was employed.[32] Diphenylphosphine borane complex (110 mg, 0.55 mmol) was dissolved in THF (5 ml), cooled to –78°C and treated with *n*-BuLi. The pale yellow solution was stirred for 30 minutes, slowly warmed to room temperature then added to a solution of **88** (100 mg, 0.38 mmol) in THF (2 ml) at 0°C. The resulting mixture was stirred overnight then quenched with water. The organic layer was washed with saturated sodium chloride, dried over magnesium sulphate and the solvent removed to give a yellow oil. Purification by flash chromatography (eluent

9:1 petroleum ether:diethyl ether) gave **90** as a clear oil (115 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.43 (3 H, dd, *J* (HH) = 7.2, *J* (PH) = 16.3, C*H*$_3$), 4.50 (1 H, dq, *J* (HH) = 7.2, *J* (PH) = 18.9, C*H*), 6.98 (1 H, tt, *J* = 7.2, *J* = 1.5, Ar-*H*), 7.07-7.29 (5 H, m, Ar-*H*), 7.45-7.54 (2 H, m, Ar-*H*), 7.73, (1 H, dt, *J* = 8.0, *J* = 1.6, Ar-*H*), 7.94 (2 H, m, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 17.2 (1 C, d, *J* (PC) = 4.5, *C*H$_3$), 35.8 (1 C, d, *J* (PC) = 32, Ar*C*H), 128-133, 138.4 (Ar); ^{31}P NMR (121.7 MHz, $CDCl_3$):δ = 26.9; ^{11}B NMR (96.4 MHz, $CDCl_3$):δ = -41.5; IR (NaCl): υ = 3066, 2359, 1471, 1436, 1105, 1062, 1026, 738, 694 cm^{-1}. *m/z* (intensity) 381 (2%), 368 (5%), 289 (55%), 183 (100%), 152 (21%), 104 (81%), 77 (79%); HRMS for $C_{20}H_{21B}BrP$: [M + NH_4-2 H] calcd 398.0839, found 398.0835.

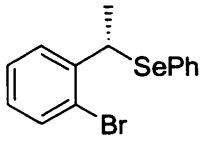
(6R, 12R, 18R)-6-12-18-Triethyl-6H, 12H, 18H, 5, 11, 17-triselena-tribenzo[a, e, i,] cyclododecane **94**



Diselenide **37** (100 mg, 0.23 mmol) was dissolved in diethyl ether (5 ml), cooled to –20°C and treated with potassium hydroxide and tosyl chloride. After stirring overnight the mixture was treated with a solution of lithium diphenyl phosphine borane complex generated by treating diphenyl phosphine borane complex (46 mg, 0.23 mmol) with *n*-BuLi (0.19 ml of a 1.6 M solution, 0.3 mmol) in hexane. The reaction was allowed to warm to room temperature and stirred for three hours. The reaction was quenched with water, diethyl ether (10 ml), added and the layers separated. The organic layer was dried over magnesium sulphate and the solvent removed. The product was purified by flash chromatography (eluent petrol) to give **94** as a red oil (37 mg, 27% yield). $[\alpha]_D$ = + 14.6 (c = 0.15 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.00 (9 H, t, *J* = 7.3, C*H*$_3$), 2.12 (6 H, m, C*H*$_2$), 5.59 (3 H, t, *J* = 7.6, Ar-*H*), 6.66 (3 H, dt, *J* = 7.3, *J* = 1.4, Ar-*H*), 7.07 (3 H, m, Ar-*H*), 7.13 (3 H, dd, *J* = 8.0, *J* = 1.2. Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ =13.8 (3x*C*H$_3$), 27.9 (3x*C*H$_2$), 47.7 (3x*C*H), 126.1 (3 C), 126.4 (3 C), 129.3

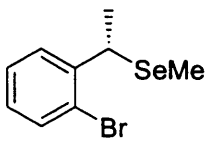
(3 C), 133.4 (3 C), 136.3 (3 C), 144.9 (3 C); ^{77}Se NMR (95 MHz $CDCl_3$):δ = 465.0; IR (NaCl): υ = 3054, 2958, 2926, 2870, 1458, 1378, 1157, 1122, 1076, 1026, 750 cm^{-1}; *m/z* (intensity) 531 (3%) [M^+], 460 (7%), 396 (15%), 307 (35%), 289 (19%), 197 (15%), 154 (100%), 136 (66%), 107 (18%); HRMS for $C_{27}H_{30}{}^{78}Se_1Se_2Br$: calcd 591.9846, found 591.9856.

(*S*)-2-(1-Phenylselanylethyl)phenyl bromide **96a**



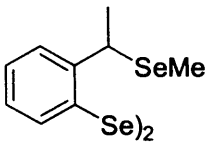
Prepared from **59a** and diphenyl diselenide by **GP 7**. Purification by MPLC (eluent:petrol) produced **96a** as a yellow oil (89 mg, 60% yield). $[\alpha]_D$ = + 48.6 (c = 1.2 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.65 (3 H, d, *J* = 7.0, C*H*$_3$), 4.80 (1 H, q, *J* = 7.0, C*H*), 6.98 (1 H, t, *J* = 7.3, Ar-*H*), 7.15-7.24 (6 H, m, Ar-*H*), 7.39 (1 H, dd, *J* = 7.9, *J* = 1.0, Ar-*H*), 7.44 (1 H, dd, *J* = 7.9, *J* = 1.0, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 22.2 (*C*H$_3$), 41.2 (*C*H), 124.4 (1 C), 127.9 (1 C), 128.4 (1 C), 128.6 (1 C), 128.6 (1 C), 129.2 (2 C), 129.2 (1 C), 133.2 (1 C), 136.1 (2 C), 142.8 (1 C); IR (NaCl): υ = 2922, 2360, 1467, 1432, 1024, 741 cm^{-1}; *m/z* (intensity): 341 (1%), 335 (3%), 186 (5%), 185 (100%) 184 (98%), 167 (10%), 149 (18%), 113 (14%), 75 (20%); HRMS for $C_{14}H_{13}SeBr$: calcd 339.9366, found 339.9364. Separation of enantiomers by HPLC (eluent 99.9:0.1 hexane:isopropanol), R_f(*S*)=19.1 min, R_f(*R*)=22.2 min.

(*S*)-1-Bromo-2-(1-methylselanyl-ethyl)-benzene **96b**



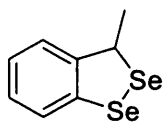
Prepared from **59a** and dimethyl diselenide by **GP 7**, purified by flash chromatography (eluent petrol) to give **96b** as a clear oil (121 mg, 64% yield). $[\alpha]_D$ = +118.4 (c = 0.5 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$):δ = 1.64 (3 H, d, *J* = 7.1, CH_3), 1.83 (3 H, s, $SeCH_3$), 4.57 (1 H, q, *J* = 7.1, C*H*), 6.99 (1 H, dt, *J* = 8.0, *J* = 1.5, Ar-*H*), 7.24 (1 H, t, *J* = 7.7, Ar-*H*), 7.41 (1 H, dd, *J* = 7.8, *J* = 1.5, Ar-*H*), 7.46 (1 H, d, *J* = 8.0, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 4.2 ($SeCH_3$), 22.0 ($CHCH_3$), 36.1 (*C*H), 124.3 (Ar), 128.2 (Ar), 128.4 (Ar), 128.6 (Ar), 133.7 (Ar), 143.6 (Ar); IR (NaCl): υ = 2963, 2922, 2863, 1588, 1563, 1468, 1437, 1374, 1272, 1175, 1052, 1021, 899, 755, 723, 661 cm^{-1}; *m/z* (intensity): 279 (7%) [M^+], 185 (84%), 183 (85%), 104 (100%), 77 (32%), 51 (18%); HRMS for $C_9H_{11}BrSe$: calcd 277.9204, found 277.9202.

Bis-[2-(1-methylselanyl-ethyl] diselenide (racemate) **98b**



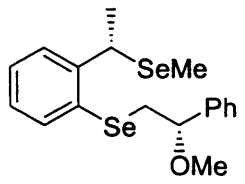
Synthesised from 1-Bromo-2-(1-methylselanyl-ethyl)-benzene by **GP 3**. Purification by flash chromatography (eluent 20:1 petroleum ether:diethyl ether) to give **98b** as a red oil (12 mg, 64% yield). ^1H NMR (400 MHz, $CDCl_3$):δ =1.62 (3 H, d, *J* = 6.8, $CHCH_3$), 1.69 (3 H, d, *J* = 7.1, $CHCH_3$), 1.81 (3 H, s, $SeCH_3$) 1.83 (3 H, s, $SeCH_3$), 4.48 (1 H, q, *J* = 7.1, C*H*), 4.52 (1 H, q, *J* = 6.8, C*H*Se), 6.95 (2 H, m, Ar-*H*), 7.14 (2 H, m, Ar-*H*), 7.23 (2 H, m, Ar-*H*), 7.65 (1 H, d, *J* = 7.7, Ar-*H*), 7.73 (1 H, d, *J* = 7.9, Ar-*H*).

3-Methyl-3*H*-benzo[1,2]-diselenacyclopentane (racemate) **99**



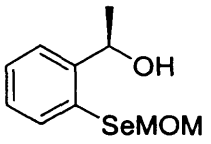
Prepared from **98** by general procedure **GP 3.** Purified by flash chromatography (eluent petroleum ether) to give **99** as a deep red oil (24 mg, 56% yield); ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.78 (3 H, d, J = 6.8, CH_3), 4.87 (1 H, q, J = 6.8, C*H*), 6.96-7.08 (3 H, m, Ar-*H*), 7.24 (1 H, dd, J = 6.9, J = 1.7, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 23.3 (*C*H$_3$), 49.7 (*C*H), 125.9 (Ar), 126.2 (Ar), 127.1 (Ar), 127.7 (Ar), 137.1 (Ar), 148.2 (Ar); ^{77}Se NMR (95 MHz $CDCl_3$):δ = 366.7, 509.8; IR (NaCl): υ = 2955, 2363, 2338, 1548, 1463, 1433, 1363, 1252, 1157, 1056, 1021, 750 cm^{-1}; *m/z* (intensity): 266 (28%), 264 (100%) [M$^+$], 262 (88%), 261 (36%), 260 (55%), 249 (65%), 247 (57%), 245 (31%), 183 (94%), 181 (46%), 103 (40%), 102 (57%), 78 (28%), 77 (36%), 63 (25%), 51 (39%); HRMS for $C_8H_8Se_2$: calcd 263.8951, found 263.8952.

1-(*SR*)-(2-{[(*SR*)-(2-Methoxy-2-phenyl)ethyl]seleno}phenyl)ethylmethylselenide **100**



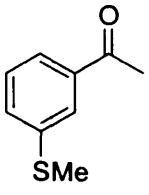
Synthesised from racemic diselenide **98b** and styrene by **GP 2.** Purification by preparative TLC (eluent 20:1 petroleum ether:diethyl ether) to give **100** as a clear oil (8 mg, 72% yield, 82% *de*). (data for major diastereomer) ^{1}H NMR (400 MHz, $CDCl_3$):δ =1.67 (3 H, d, J = 7.0, CHCH_3), 1.81 (3 H, s, SeCH_3), 3.03 (1 H, dd, J = 12.2, J = 4.9, SeC*H*H), 3.17 (3 H, s, OCH_3), 3.21 (1 H, dd, J = 12.3, J = 8.7, SeCH*H*), 4.26 (1 H, dd, J = 8.8, J = 4.7, C*H*OCH$_3$), 4.69 (1 H, q, J = 7.0, C*H*CH$_3$), 7.01 (1 H, dt, J = 7.7, J = 1.0, Ar-*H*), 7.14-7.33 (7 H, m, Ar-*H*), 7.42 (1 H, d, J = 7.7, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 4.2 (Se*C*H$_3$), 22.3, (CH*C*H$_3$), 36.2 (Se*C*H$_2$), 36.7 (O*C*H$_3$) 57.4 (O*C*H$_3$), 83.4 (PhCHOCH$_3$); *m/z* 414 (38%) [M$^+$], 399 (49%), 319 (4%), 287 (55%), 279 (95%), 206 (3%), 183 (79%), 135 (53%), 121 (52%), 103 (100%), 91 (85%), 77 (42%), 59 (15%), 51 (33%), 43 (39%). Major diastereoisomer assigned by comparison with oxygen and sulphur analogues.

(*R*)-1-(2-Methoxymethylselanylbenzene)ethanol **105**



Prepared from **59** and **61** by **GP 3.** Purification by flash chromatography (eluent 4:1 petroleum ether:diethyl ether) gave **105** as a yellow oil (54 mg, 67% yield). $[\alpha]_D$ = -29.2 (c = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$):δ = 1.41 (3 H, d, J = 6.8, $CHCH_3$), 2.60 (1 H, br, O*H*), 3.33 (3 H, s, OCH_3), 5.08 (2 H, s, CH_2), 5.23 (1 H, q, J = 6.8, C*H*), 7.12 (1 H, dt, J = 6.4, J = 1.2, Ar-*H*), 7.25 (1 H, dt, J = 8.0, J = 1.2, Ar-*H*), 7.46 (1 H, dd, J = 7.6, J = 1.2, Ar-*H*), 7.61 (1 H, dd, J = 7.6, J = 1.2, Ar-*H*);^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 23.6 (CH_3), 57.6 (OCH_3), 69.3 (*C*H), 75.4 (CH_2), 126.0 (1 C), 128.6 (1 C), 128.7 (1 C), 129.8 (1 C), 135.0 (1 C), 147.7 (1 C); ^{77}Se NMR (95 MHz $CDCl_3$) δ = 285.6; IR (NaCl): υ = 2920, 1448, 1273, 1180, 1085, 926, 877, 757 cm^{-1}; *m/z* (intensity) 246 (100%) [M^+], 229 (63%), 214 (10), 199 (7%), 184 (14%), 122 (12%), 104 (5%); HRMS for $C_{10}H_{14}O_2Se$ calcd: 246.0154, found 246.0156.

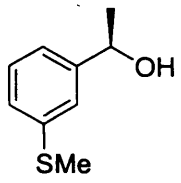
3-(Thiomethyl)acetophenone **108**



3-bromoacetopheneone (1 g, 5 mmol) was dissolved in THF (10 ml) cooled to –78°C and treated with *t*-BuLi (1.5 M, 10 ml, 15 mmol). The reaction was slowly warmed to room temperature and stirred for 90 minutes before dimethyl disulphide (0.94 mg, 10 mmol) was added. After stirring for a further 2 hours, HCl (20 ml, 1M) was added and the product extracted into diethyl ether. The organic layer was washed with saturated sodium chloride, dried over magnesium sulphate and the solvent removed. Purification

by flash chromatography (eluent 20:1 petrol:diethyl ether) gave **108** as a clear oil (315 mg, 38% yield). Spectroscopic data consistent with published data.[102]

(*R*)-3-(Thiomethyl)phenylethanol **109**



Prepared from **108** and dimethyl disulphide by **GP 5**. Purification by flash chromatography (eluent 2:1 petrol:diethyl ether) to give **109** as a clear oil (84% yield, 97% *ee.*) $[\alpha]_D$ = +30.6 (c = 0.9 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$):δ =1.38 (3 H, d, J = 6.5, CH_3), 2.40 (3 H, s, SCH_3), 4.86 (1 H, q, J = 6.5, C*H*), 7.02-7.07 (2 H, m, Ar-*H*), 7.11-7.21 (2 H, m, Ar-*H*);^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 16.1 (CH_3), 25.5 (SCH_3), 70.6 (PhCH), 122.5 (1 C), 123.8 (1 C), 125.7 (1 C), 129.3 (1 C), 139.0 (1 C), 147.0 (1 C); IR (NaCl): υ = 3407, 2975, 1591, 1473, 1423, 1368, 1204, 1112, 1076, 1009, 908, 784, 699 cm^{-1}; *m/z* (intensity) 169 (16%), 168 (100%) [M^+], 153 (17%), 151 (44%), 125 (49%), 110 (11%), 109 (49%), 73 (37%), 57 (14%); HRMS for $C_9H_{12}OS \bullet NH_4$: calcd 186.0947, found 186.0945. Separation of enantiomers by HPLC (eluent 99:1 hexane:isopropanol), R_f (*S*)=44.7 min, R_f (*R*)=48.1 min. Absolute stereochemistry assigned by comparison with 1-(3-methoxyphenyl)ethanol.[37] The racemate was synthesised from **108** by **GP 6** (93% yield) for HPLC reference.

Appendix 1-Glossary of terms used in Electrochemistry

Anode
The electrode where oxidation occurs in an electrolytic cell.

Cathode
The electrode where reduction occurs in an electrolytic cell.

Current

The movement of electrical charges as carried by electrons in a conductor or ions in an electrolyte, measured in amperes. In electrochemistry it is direct current that is almost exclusively used.

Cyclic Voltammetry
A cyclic voltammetry experiment can be used to establish the oxidation potential of a compound. During this experiment, the potential of the cell is varied over a defined range and the current flow recorded. Most often a triangular potential-time waveform with equal positive and negative slopes is used, with the initial and final potentials the same. When the oxidation potential of the substrate is reached by the cell potential, the substrate is oxidised, resulting in a surge in the flow of electrons recorded as an increase in the current by the potentiostat. The location of the peak indicates the oxidation potential, given as a value relative to a reference electrode. As an additional reference, an additive may be added to the solution whose oxidation potential is known. A commonly used standaed is the ferrocene/ferrocenium redoc couple. As the potential is reduced, a negative signal may be generated if the oxidation is reversible, corresponding to the reduction of the oxidised species.

Dipole
A pair of equal and opposite charges separated by a small distance, for example within a molecule. This enables the molecule to become aligned when an electric field is applied, reducing the electrical resistance of the cell.

Electrolyte
A chemical compound that dissociates into electrically charged ions when dissolved in a solvent. The resulting solution is an ionic conductor of electricity

Electrochemical Cell

This consists of two electronically conducting phases, in this case solid electrodes and an organic solution containing an electrolyte, where an electrical current can pass, changing to an ionic current as it passes through the solution and back to an electrical current at the electrode.

Electrolytic Cell

An electrochemical cell that converts electrical energy into chemical energy. Current is provided from an external source and is used to drive non-spontaneous reactions at the electrodes. It is in this type of cell that electrolysis takes place. The cell used in this investigation is shown below.

Faraday

The Faraday (F) is the charge on 1 mol of electrons (i.e. 6.022×10^{23} electrons) given in Coulombs. The number of Faradays used in a reaction is calculated by the following equation;

$$\frac{\text{Reaction time (s) X Current (mA)}}{\text{96484 C (charge on 1 mol of electrons)}} = nF$$

The value F/mol is simply the above equation divided by the number of moles of the substrate used in the reaction.

Galvanic Cell

An electrochemical cell that converts chemical energy into electrical energy by spontaneous reactions that occur at the electrodes which are connected by an external circuit, producing electrical current.

Resistance

A measurement of the inability of a material to carry electrical current, the greater the resistance the greater this inability.

Potential

Sometimes used interchangeably with "voltage", the potential is the force exerted by a fixed point of charge on surrounding charges. In the case of an electrochemical cell, this fixed point is generated by the potentiostat.

[1]. Kolbe, H. *Ann. Chim.* **1849**, *69*, 257.

[2]. Lund, H., Hammerich, O. *Organic Electrochemistry* 4th ed. **2001**, Basel: Marcel Dekker, p3.

[3]. Schäfer, H. *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 911.

[4]. Baizer, M. M. *J. Electrochem. Soc.* **1964**, *215*, 111.

[5].Pütter, H. in *Organic Electrochemistry* 4th ed. (eds. Lund, H., Hammerich, O.), **2001**, Basel: Marcel Dekker, p1277.

[6].Sock, O., Troupel, M., Perichon, J. *Tetrahedron Lett. 1985*, *26*, 1509.

[7]. Cerefice, S. A., Fields, E. K. *J. Org. Chem.* **1974**, *39*, 971.

[8]. Nilsson, A., Palmquist, U., Pettersson, T., Ronlan, A. *J. Chem. Soc. Perkin Trans. 1* **1978**, *7*, 708.

[9].Pütter, H. in *Organic Electrochemistry* 4th ed. (eds. Lund, H., Hammerich, O.), **2001**, Basel: Marcel Dekker, chapter 31 and references therin.

[10]. Hammerich, O. in *Organic Electrochemistry* 4th ed. (eds. Lund, H., Hammerich, O.), **2001**, Basel: Marcel Dekker, p96.

[11]. Nonaka, T., Fuchigami, T. in *Organic Electrochemistry* 4th ed. (eds. Lund, H., Hammerich, O.), **2001**, Basel: Marcel Dekker, p1052.

[12]. Little, R. D. *Chem. Rev.* **1996**, *93*, 96.

[13]. Nonaka, T., Fuchigami, T. in *Organic Electrochemistry* 4th ed .(eds. Lund, H., Hammerich, O.), **2001**, Basel: Marcel Dekker, p1054.

[14]. Simonet, J., Pilard, J. *Organic Electrochemistry* 4th ed .(eds. Lund, H., Hammerich, O.), **2001**, Basel: Marcel Dekker, p1163

[15]. Skarzewski, J. *Tetrahedron* **1984**, *40*, 4997.

[16]. Torii, S., Liu, P., Bhuvaneswari, N., Amatore, C., Jutland, D. *J. Org. Chem.* **1996**, *61*, 3055.

[17]. Berrisford, D. J., Bolm, C., Sharpless, K. B. *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 1059.

[18]. Viertler, H., Gruber, J., Pardini, V. L. in *Organic Electrochemistry* 4th ed. (eds. Lund, H., Hammerich, O.), **2001**, Basel: Marcel Dekker, p621-668.

[19]. Maeda, H., Ohmori, H. *Acc. Chem. Res.* **1999**, *32*, 72.

[20]. Fuchigami, T., Surowiec, K. *J. Org. Chem.* **1992**, *57*, 5781.

[21]. Fuchigami, T., Yammamoto, K., Nakagawa, Y. *J. Org. Chem.* **1991**, *56*, 137.

[22]. (a) Reich, H. J., Chow, F., Shah, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 846; (b) Ponthieux, S., Paulmier, *Topics in Current Chemistry*, **2000**, *208*, 118.

[23]. Torii, S., Uneyama, K., Handa, K. *Tetrahedron Lett.* **1980**, *21*, 1863.

[24]. (a) Clive, D. L. *Tetrahedron* **1978**, *34*, 1049; (b) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

[25]. Ponthieux, S., Paulmier, C. in *Topics in Current Chemistry*, **2000**, *208*, 114-141.

[26]. Bewick, A., Coe, D. E., Fuller, G. B., Mellor, J. M. *Tetrahedron Lett.* **1980**, *21*, 3827.

[27]. Toshimitsu, A., Aoai, T., Owada, H., Uemura, S., Okano, M. *J. Org. Chem.* **1981**, *46*, 4727.

[28]. Torii, S., Uneyama, K., Takano, K. *Tetrahedron Lett.* **1982**, *21*, 1161.

[29]. Reich, H. J., Renga, J. M., Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

[30]. Smith, D. S., Winnik, J., Ding, Y., Bottomley, L. A. *Electrochimica Acta*, **1998**, *43*, 335.

[31]. Inokuchi, T., Kusumoto, M., Torii, S. *J. Org. Chem.* **1990**, *55*, 1548.

[32]. Torii, S., Uneyama, K., Ono, M. *Tetrahedron Lett.* **1980**, *21*, 2741.

[33]. Konstantinović, S., Vukićević, R., Mihailović, M. L. *Tetrahedron Lett.* **1987**, *28*, 6511.

[34]. Torii, S. Uneyama, K. Ono, M. *J. Am. Chem. Soc.* **1981**, *103*, 4604.

[35]. Nicolaou, K. C., Petasis, N. A. *Selenium in Natural Product Synthesis*, CIS, Philadelphia **1984**.

[36]. Drabowicz, J., Mikolajczyk, M. in *Topics in Current Chemistry*, **2000**, *208*, 143-174.

[37]. Sharpless, K. B., Young, M. W., Lauer, R. F. *Tetrahedron Lett.* **1973**, *22*, 1979.

[38]. Clive, D., Chittattu, G. J., Farina, V., Kiel, W. A., Menchen, S. M., Russell, G. C., Singh, A., Wong, C. K., Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438.

[39]. Jones, D. N., Mundy, D., Whitehouse, R. D. *J. Chem. Soc. Chem. Comm.* **1970**, 86.

[40]. Tomoda, K., Iwakao, M. *Chem. Lett.* **1988**, 1895.

[41]. Wirth, T. *Tetrahedron* **1999**, *55*, 1; (b) Wirth, T. *Angew. Chem. Int. Ed. Eng.* **2000**, *112*, 3740.

[42]. (a) Jackson, W. P., Ley, S. V., Whittle, A. J. *J. Chem. Soc. Chem. Comm.* **1980**, 1173; (b) Back, T. G., Muralidharan, K. R. *J. Org. Chem.* **1991**, *56*, 2781; (c) Murata, S., Suzuki, T. *Tetrahedron Lett.* **1987**, *28*, 4415.

[43]. Nishibayashi, N., Uemura, S. *Topics in Current Chemistry*, **2000**, *208*, 235-255.

[44]. Tiecco, M., Testaferri, L., Bagnoli, C., Santi, C. *J. Chem. Soc. Chem. Comm.* **1993**, 637.

[45]. Iwako, M., Tomoda, S. *J. Chem. Soc. Chem. Comm.* **1992**, 1165.

[46]. Wirth, T., Häuplti, S., Leuenberger, M. *Tetrahedron Asym.* **1998**, *9*, 547.

[47]. (a) Déziel, R., Goulet, S., Grenier, L., Bordeleau, J., Bernier, J., *J. Org. Chem. 1994*, *58*, 3619; (b) Déziel, R., Malenfant, E., Bélanger, G., *J. Org. Chem.* **1996**, *60*, 4114.

[48]. Back, T. G., Dyck, B. P., Parvez, M. *J. Chem. Soc. Chem. Comm.* **1994**, 515.

[49]. Iwaoka, M., Tomoda, S., *J. Am. Chem. Soc.* **1996**, *118*, 8077.

[50]. Nishibayashi, Y., Singh, J. D., Uemura, S., Fukuzawa, S. *Tetrahedron Lett.* **1994**, *35*, 3115.

[51]. Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1726.

[52]. Fragale, G., Neuburger, M., Wirth, T. *J. Chem. Soc. Chem. Comm.* **1998**, 1867.

[53]. a) Tiecco, M., Testaferri, L., Bagnoli, L., Marini, F., Temperini, A., Tomassini, C., Santi, C. *Tetrahedron Lett.* **2000**, *41*, 3241; (b) Tiecco, M., Testaferri, L., Santi, C., Tomassini, C., Marini, F., Bagnoli, L., Temperini, A. *Chem. Eur. J.* **2002**, *8*, 1118.

[54]. Wirth, T., Fragale, G. *Chem. Eur. J.* **1997**, *3*, 1894.

[55]. Horowitz, H. H. *J. App. Electrochem.* **1984**, *14*, 779.

[56] Kojima, K., Sakuragi, H., Tokumaru, K. *Chem. Lett.* **1981**, 1707.

[57] Schäfer, H. J. in *Organic Electrochemistry* 4th ed. (eds. Lund, H., Hammerich, O.), **2001**, Basel: Marcel Dekker, p909.

[58]. a) Tomoda, S., Iwaoka, M. *J. Am. Chem. Soc.* **1996**, *118*, 8077; (b) Komatsu, H., Iwaoka, M., Tomoda, S. *J. Chem. Soc. Chem. Comm.* **1999**, 205; (c) Mugesh, G., Singh, H. B., Butcher, R. J. *Tetrahedron: Asymm.* **1999**, *10*, 237; (d) Mugesh, G., Panda, A., Singh, H. B., Butcher, R. J. *Chem. Eur. J.* **1999**, *5*, 1411; (e) Spichty, M., Fragale, G., Wirth, T. *J. Am. Chem. Soc.* **2000**, *122*, 10914.

[59]. Uehlin, L., Wirth, T. *Org. Lett.* **2001**, *3*, 2931.

[60]. Uehlin, L., Wirth, T. *Phosphorous Sulphur* **2001**, *172*, 189.

[61]. Miyashita, M., Hoshino, M., Yoshikoshi, A., *Tetrahedron Lett.* **1998**, *29*, 347; (b) Miyashita, M., Suzuki, T., Hoshino, M., Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12496.

[62]. Blanco, J. M., Caamaño, O., Eirín, Fernández, F., Medina, L. *Synthesis* **1990**, 584.

[63]. Dimitrov, V., Genov, M., Simova, S., Linden, A. *J. Organomet. Chem.* **1996**, *525*, 213.

[64]. Uno, M., Ando, K., Komatsuzaki, N., Tsuda, T., Sawada, M., Takahashi, S. *J. Organomet. Chem.* **1994**, *473*, 303.

[65]. Uehlin, L., Fragale, G., Wirth, T. *Chem. Eur. J.* **2002**, *8*, 1125.

[66]. King, R.B., Bakos, J., Hoff, C.D., Marko, L. *J. Org. Chem.* **1979**, *10*, 1979.

[67]. Longmire, J.M., Zhang, X., Shang, M. *Organometallics* **1998**, *20*, 4374.

[68]. Stang, P. J., Hanak, M., Subramanian, L. R. *Synthesis* **1982**, 85.

[69]. Screttas, C. G., Heropoulos, G. A., Micha-Screttas, M., Steele, B. R., Catsoulacos, D. P. *Tetrahedron Lett.* **2003**, *44*, 5633.

[70]. a) Krief, A., Trabelsi, M., Dumont, W. *Synthesis* **1992**, 933; b) Liotta, D., Markiewcz W., Santiesteban, H. *Tetrahedron Lett*, **1977**, 4365.

[71]. Ley, S. V., O'Neil, I. A., Low, C. M. R. *Tetrahedron Lett.* **1986**, *42*, 5363.

[72]. Reich, H. J., Renga, J. M., Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

[73]. Knochel, P., Dohle, W., Gommermann, N., Kniesel, F. F., Kopp, F., Korn, T., Sapountzis, I., Vu, V. A. *Angew Chem. Int. Ed.* **2003**, *42*, 4302.

[74]. Ahlbrecht, H., Ibe, M., *Synthesis* **1988**, *3*, 216.

[75]. Brown, H. C., Chandrasekharan, J., Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.

[76]. Hoye, T. R., Richardson, W. S. *J. Org. Chem.* **1989**, *54*, 693.

[77]. Pak, C. S., Lee. E., Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523.

[78]. Goossen, L. J., Ghosh, K. *Eur. J. Org. Chem.* **2002**, *19*, 3254.

[79]. Moon, H., Schore, N. E., Kurth. M. J. *J. Org. Chem.* **1992**, *57*, 6088.

[80]. Lars Uehlin, PhD thesis, University of Basel, **2002**.

[81]. Tiecco, M., Testaferri, L., Tingoli, M., Chianelli, D., Bartoli, D. *Tetrahedron* **1988**, *44*, 2261.

[82]. Wilkins, C. L., Regulski, T. W. *J. Am. Chem. Soc.* **1972**, *94*, 6016.

[83]. Kaufman, M. J., Streitwieser, A. *J. Am. Chem. Soc.* **1987**, *109*, 6092.

[84]. Ruasse, M. F., Argile, A., Dubois, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 7645.

[85]. Uemura, S., Fukuzawa, S. *J. Am. Chem. Soc.* **1983**, *105*, 2748.

[86]. Clawson, P., Lunn, P. M., Whiting, D. A. *J. Chem. Soc. Perkin 1*, **1990**, 159.

[87]. Tiecco, M., Testaferri, L., Marini, F., Santi, C., Bagnoli, L., Temperini, A. *Tetrahedron Asym.* **1999**, *10*, 747.

[88]. Burgess, K., Porte, A. M. *Angew. Chem.* **1994**, *106*, 1218.

[89]. Evans, D., Michael, F. E., Tedrow, J. R., Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534.

[90]. Uehlin, L., Wirth, T. *Phosphorous Sulphur* **2001**, *172*, 189.

[91]. Davies, S. G., Goodfellow, C. L., Sutton, K. H. *Tetrahedron Asym.* **1992**, *10*, 1303.

[92]. Galynker, I., Still, W. C. *Tetrahedron Lett.* **1982**, *43*, 4461.

[93]. Bernardi, L., Bonini, B. F., Comes-Franchini, M., Fochi, F., Mazzanti, G., Ricci, A., Varchi, G. *Eur. J. Org. Chem.* **2002**, *8*, 2776.

[94]. Dimitrov, V., Genov, M., Simova, S., Linden, A. *J. Oranogmet. Chem.* **1996**, *525*, 213.

[95]. Wakatsuki, Y., Yamazaki, H. *Inorg. Synth.* **1989**, *26*, 190.

[96]. Mabrouk, S. T., Rausch, M. D. *J. Organomet.Chem.* **1996**, *523*, 111.

[97]. Noe, C. R., Knollmueller, M., Dungler, K., Miculka, C. *Chem. Ber.* **1994**, *127*, 359.

[98]. Ueda, I., Umio, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2323.

[99]. Halpern, M. *Org. Prep. Proced.* **1976**, *8*, 299.

[100]. Jones, P. R., Shelnut, J. G. *J. Org. Chem.* **1979**, *44*, 696.